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Synthetic studies toward Eurycolactone C

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Synthetic studies toward Eurycolactone C

by

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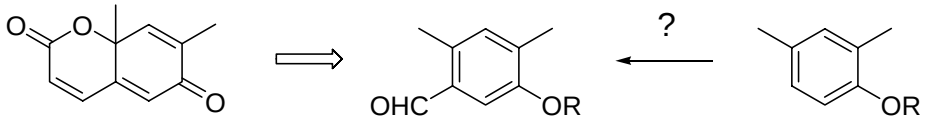
GENERAL INTRODUCTION

Over the last decades, organic synthesis has played an essential role in the pharmaceutical industry. The development of synthetic methodologies and strategies allow us to access complex natural products in an efficient way and fuel the drug discovery. Chapter one describes the study of aryl triflates and aryl pivalates reactions with electrophiles and provides extensive information about the regioselectivities of the reactions. Chapter two introduces a novel method to generate 6- and 8-substituted 1-methoxynaphthalene (or α-naphthol). Chapter three describes synthetic studies toward eurycolactone C.

Chapter 1. The study of aryl triflates and aryl pivalates reactions with electrophiles - the triflate and pivalate as a *meta*-directing group[1]

Introduction



In the course of a synthesis of eurycolactone C,[2] we required a direct route to the lactone. After evaluating several possibilities, the *meta*-hydroxy aldehyde emerged as a direct precursor. Although 2,4-dimethylphenol (R=H) is inexpensive and readily available, electrophilic acylation would be expected to provide the *ortho*-hydroxy aldehyde rather than the *meta*-hydroxy aldehyde. We protected the phenol with groups that converted the phenol into a net electron-withdrawing group and studied the reactions of these compounds with electrophiles.

Electrophilic aromatic substitutions have been studied for decades and have become the very important class of reactions that allow the introduction of substituents on arenes.[3] The directing effects of substituents on the arenes are well established.

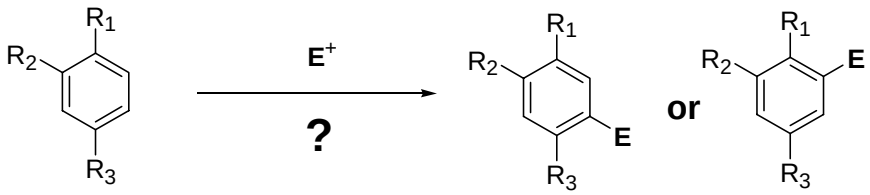
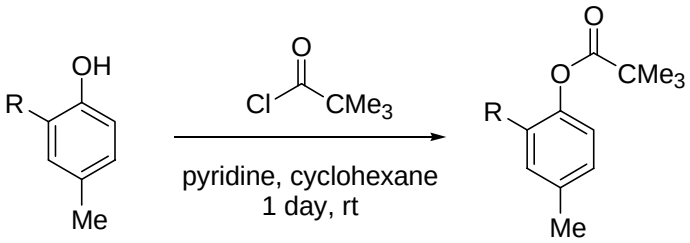


Figure 1

Hence, *ortho-para* directing groups and *meta* directing groups are well discussed in the most organic text books. However, the regioselectivity of electrophilic substitutions on multi-substituted benzenes is not always easy to predict. We tested various electrophilic substitutions on pivalates and triflates of multi-substituted phenols.

Results and Discussion



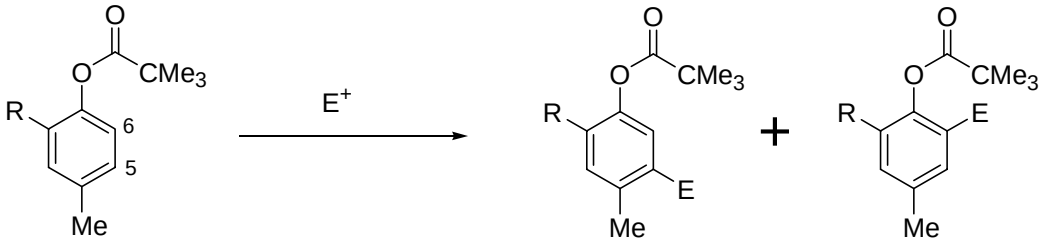
1a, R = Me
1b, R = OMe
1c, R = Br
1d, R = H

2a, R = Me 87%
2b, R = OMe 91%
2c, R = Br 93%
2d, R = H 86%

Scheme 1

Pivalates were made from alcohols (**1a**, **1b**, **1c** and **1d**) with pivaloyl chloride and pyridine in cyclohexane (Scheme 1). Each pivalate was purified by a flash column chromatography.

Table 1. Reaction of pivalates with electrophiles



2a-d

3 **4**

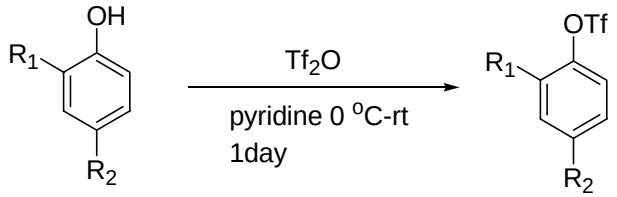
2a, R = Me
2b, R = OMe
2c, R = Br
2d, R = H

Entry	R	$\mathbf{E}^+$	% yield	% yield
a	Me	$MeOCHCl_2$, $TiCl_4$, CH_2Cl_2, 0 ^oC-rt, 12h	76(**3a**)	0
b	Me	Br_2, AcOH, rt, 12h	64(**3b**)	0
c	Me	iPrBr, $AlCl_3$, $ClCH_2CH_2Cl$, rt	0	0
d	Me	AcCl, $AlCl_3$, $ClCH_2CH_2Cl$, rt	0	0
e	MeO	$MeOCHCl_2$, $TiCl_4$, CH_2Cl_2, 0 ^oC-rt, 12h	23(97)*(**3e**)	0
f	Br	$MeOCHCl_2$, $TiCl_4$, CH_2Cl_2, 0 ^oC-rt, 12h	0	0
g	Br	Br_2, AcOH, rt, 12h	0	0
h	H	Br_2, AcOH, rt, 12h	0	30(98)*(**4h**)

***** Conversion yield shown in parenthesis

Electrophilic aromatic substitutions of pivalates are shown in Table 1. The electrophilic substitution reactions of 2,4-dimethylphenyl pivalate exclusively occurred at the *meta* (C-5)

position in the formylation and the bromination[4] reactions. However, we did not obtain any product in the akylation[5] and the acylation[6] reactions. The structures of aldehyde **3a** and bromide **3b** were determined by ^{1}H NMR, ^{13}C NMR and 2D NOESY NMR. The regiochemistry of aldehyde **3a** and bromide **3b** were determined by 2D NOESY NMR. Only one aromatic proton exhibited NOE interaction with the methyl group at C-4. Formylation of 2-methoxy-4-methylphenyl pivalate (**2b**) also occurred *meta* to the pivalate. By contrast to the other pivalates, the bromination of 4-methylphenyl pivalate provided 2-bromo-4-methylphenyl pivalate (**4h**) which was identical to pivalate **2c** by ^{1}H NMR.



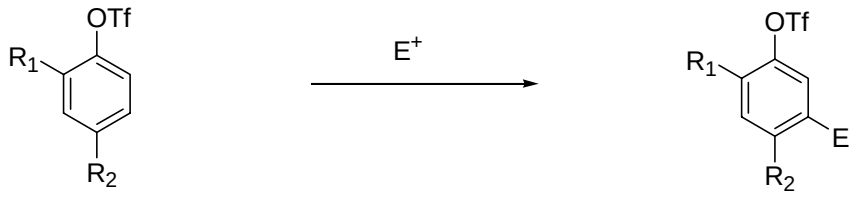
1a, R_1 = Me, R_2 = Me
1b, R_1 = OMe, R_2 = Me
5c, R_1 = OMe, R_2 = Br
5d, R_1 = OMe, R_2 = H

6a, R_1 = Me, R_2 = Me 92%
6b, R_1 = OMe, R_2 = Me 97%
6c, R_1 = OMe, R_2 = Br 91%
6d, R_1 = OMe, R_2 = H 93%

Scheme 2

Triflates was obtained from alcohols with trifluoromethanesulfonic acid anhydride in pyridine.[7] With the triflates in hand, we tested electrophilic substitution reactions on each triflate.

Table 2. Reaction of triflates with electrophiles

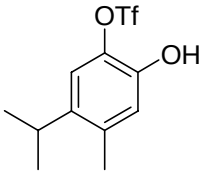


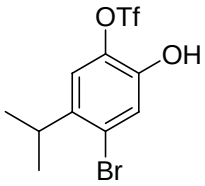
6a-d **7**

6a, R_1 = Me, R_2 = Me
6b, R_1 = OMe, R_2 = Me
6c, R_1 = OMe, R_2 = Br
6d, R_1 = OMe, R_2 = H

Entry	R_1	R_2	$\mathbf{E}^+$	% yield
a	Me	Me	$MeOCHCl_2$, $TiCl_4$, CH_2Cl_2, 0 ^oC-rt, 12h	41(**7a**)
b	Me	Me	Br_2, AcOH, rt, 12h	0
c	MeO	Me	$MeOCHCl_2$, $TiCl_4$, CH_2Cl_2, 0 ^oC-rt, 12h	96(**7c**)
d	MeO	Me	Br_2, AcOH, rt, 12h	100(**7d**)
e	MeO	Me	iPrBr, $AlCl_3$, $ClCH_2CH_2Cl$, rt	51[a](**7e**)
f	MeO	Me	AcCl, AlCl3, $ClCH_2CH_2Cl$, rt	95(**7f**)
g	MeO	Br	$MeOCHCl_2$, $TiCl_4$, CH_2Cl_2, 0 ^oC-rt, 12h	47(**7g**)
h	MeO	Br	Br_2, AcOH, rt, 30h	97(**7h**)
i	MeO	Br	iPrBr, $AlCl_3$, $ClCH_2CH_2Cl$, rt,	42[b](**7i**)

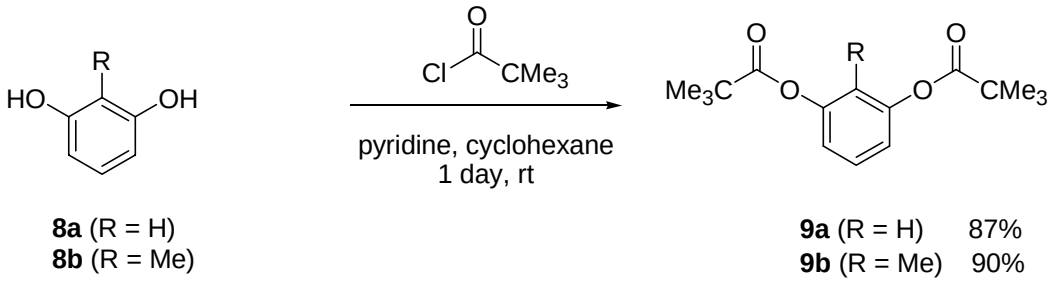
j	MeO	Br	AcCl, $AlCl_3$, $ClCH_2CH_2Cl$, rt	29(**7j**)
k	MeO	H	$MeOCHCl_2$, $TiCl_4$, CH_2Cl_2, 0 ^oC-rt, 12h	99(**7k**)
l	MeO	H	AcCl, $AlCl_3$, $ClCH_2CH_2Cl$, rt	94(**7l**)

a, 34% 

b, 56% 

The electrophilic aromatic substitutions of triflates are shown in Table 2. The formylation of 2,4-dimethylphenyl triflate showed the substitution *meta* to the triflate to provide aldehyde **7a** in 41% yield. The electrophilic substitutions (formylation, bromination and acylation) of 2-methoxy-4-methylphenyl triflate (**6b**) occurred *meta* to the triflate in excellent yield. Interestingly, we obtained product **7e** and an unexpected byproduct, 2-hydroxy-5-isopropyl-4-methylphenyl triflate in the alkylation reaction.

The electrophilic substitutions of 4-bromo-2-methoxyphenyl triflate (**6c**) showed that the substitutions exclusively occurred *meta* to the triflate in the formylation, the bromination reaction, the alkylation and the acylation reactions. In the alkylation of 4-bromo-2-methoxyphenyl triflate, we isolated a demethylated byproduct, 4-bromo-2-hydroxy-5-isopropylphenyl triflate and product **7i**. The formylation and the acylation of 2-methoxyphenyl triflate provided products *meta* to the triflate in 99% and 94% yield, respectively.

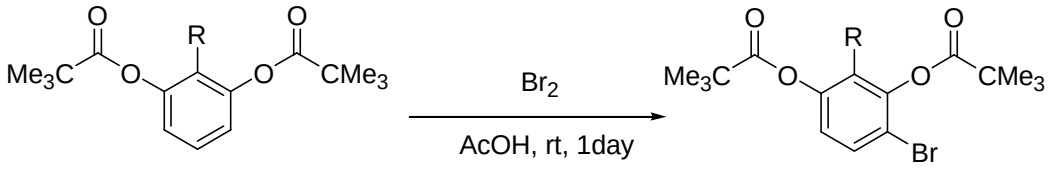


8a (R = H)
8b (R = Me)

9a (R = H) 87%
9b (R = Me) 90%

Scheme 3

The steric hinderance of the pivaloyl protecting group might not allow electrophiles to substitute at the *ortho*-position. Therefore, we carried out the substitution reactions on pivalates of resorcinol and 2-methyl resorcinol.



9a (R = H)
9b (R = Me)

10a (R = H) 92%
10b (R = Me) 93%

Scheme 4

However, we found that neither of the pivalates formed the *meta*-substituted products in the bromination reaction (Scheme 4). The reactions gave brominated products **10a** and **10b,** instead.

In conclusion, we tested the electrophilic aromatic substitutions on pivalates and triflates of multi-substituted phenols and we determined the regioselectivities of the reactions. Moreover, the use of aryl triflates to control the regiochemistry of intermolecular acylation,

bromination or alkylation should have broad application. The ease of triflate introduction coupled with the well-established organometallic chemistry of aryl triflates[8] combine to offer many avenues for elaboration.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane and benzene were distilled over calcium hydride. All experiments were performed under argon atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.27 ppm for ^1H and 77.23 ppm for ^{13}C), unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 A, 32-63 μm) was used for a flash column chromatography.

General procedure for the pivalation reaction

To a solution of the phenol (1.0 equiv.) in cyclohexane (0.1 M) was added pyridine (1.4 equiv.) followed by pivaloyl chloride (1.4 equiv.) at rt under argon. The resulting mixture

was stirred for 1 day. The mixture was poured into water, diluted with Et_2O, washed sequentially with 1N HCl, 1N NaOH and water, dried over $MgSO_4$, concentrated in vacuum and purified by a flash column chromatography to afford pivalate.

2,2-Dimethylpropionic acid 2,4-dimethylphenyl ester (2a)

Isolated in 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H), 7.00 (d, *J* = 8 Hz, 1H), 6.84 (d, *J* = 8 Hz, 1H), 2.31 (s, 3H), 2.13 (s, 3H), 1.38 (s, 9H).

2,2-Dimethylpropionic acid 2-methoxy-4-methylphenyl ester (2b)

Isolated in 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (d, *J* = 8.0 Hz, 1H), 6.76(s, 1H), 6.74 (d, *J* = 8 Hz, 1H), 3.79 (s, 3H), 2.35 (s, 3H), 1.37 (s, 9H).

2,2-Dimethylpropionic acid 2-bromo-4-methylphenyl ester (2c)

Isolated in 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.42 (d, *J* = 1.2 Hz, 1H), 7.11 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 2.34 (s, 3H), 1.40 (s, 9H).

2,2-Dimethylpropionic acid *p*-tolyl ester (2d)

Isolated in 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.18 (d, J = 8 Hz, 2H), 6.94 (d, J = 8 Hz, 2H), 2.35 (s, 3H), 1.37 (s, 9H).

2,2-Dimthylpropionic acid 3-(2,2-dimethylpropionyloxy)-phenyl ester (9a)

Isolated in 87% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (t, *J* = 8.1 Hz, 1H), 6.95 (dd, *J* = 8.1 Hz, *J* = 2.1 Hz, 2H), 6.87 (t, *J* = 2.1 Hz, 1H), 1.36 (s, 18H).

2,2-Dimethylpropionic acid 3-(2,2-dimethylpropionyloxy)-2-methylphenyl ester (9b)

Isolated in 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (t, *J* = 8.1 Hz, 1H), 6.90 (d, *J* = 8.1 Hz, 2H), 1.99 (s, 3H), 1.39 (s, 18H).

General procedure for the triflation reaction

To a solution of the phenol (1.0 equiv.) in pyridine (0.3 M) was slowly added triflic anhydride (1.5 equiv.) at 0 ^{o}C under argon. The resulting mixture was stirred for 1 day while allowing it to warm to rt. The mixture was poured into water, diluted with Et_2O, washed sequentially with water, 10% aqueous HCl and brine, dried over $MgSO_4$, concentrated in vacuum and purified by a flash column chromatography to afford triflate.

Trifluoromethanesulfonic acid 2,4-dimethylphenyl ester (6a)

Isolated in 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14-7.08 (m, 2H), 7.05 (dd, *J* = 8 Hz, *J* = 2 Hz, 1H), 2.35 (s, 3H), 2.34 (s, 3H).

Trifluoromethanesulfonic acid 2-methoxy-4-methylphenyl ester (6b)

Isolated in 97% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 1.2 Hz, 1H), 6.77 (dd, *J* = 8.4 Hz, *J* = 1.2 Hz, 1H), 3.90 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 139.9, 136.9, 122.2, 121.5, 119.0 (q, *J* = 318 Hz), 114.1, 56.3, 21.7.

Trifluoromethanesulfonic acid 4-bromo-2-methoxyphenyl ester (6c)

Isolated in 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 2.0 Hz, 1H), 7.13 (dd, *J* = 8.8 Hz, *J* = 2.0 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 3.93 (s, 3H).

Trifluoromethanesulfonic acid 2-methoxyphenyl ester (6d)

Isolated in 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dt, *J* = 7.6, *J* = 1.2 Hz, 1H), 7.23 (dd, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 7.05 (dd, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 6.99 (dt, *J* = 7.6, *J* = 1.2 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 138.8, 129.3, 122.5, 120.9, 118.8 (q, *J* = 318 Hz), 113.2, 56.1.

General procedure for the formylation of pivalate and triflate

To a solution of the pivalate or triflate (1.0 equiv.) in CH_2Cl_2 (0.1 M) was added $CHCl_2OMe$ (1.5 equiv.) followed by $TiCl_4$ (2.8 equiv.) at 0 ^{o}C under argon. The reaction mixture was warmed to rt. After being stirred at rt for 12 h, The mixture was poured into ice water, washed with sat. $NaHCO_3$, dried over $MgSO_4$, concentrated in vacuum and

purified by a flash column chromatography to afford aldehyde.

2,2-Dimethylpropionic acid 5-formyl-2,4-dimethylphenyl ester (3a)

Isolated in 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 7.42 (s, 1H), 7.13 (s, 1H), 2.63 (s, 3H), 2.21 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 176.8, 148.2, 138.2, 137.2, 134.7, 133.2, 124.7, 39.4, 27.4, 18.9, 16.6; HRMS *m/e* (EI) for $C_{14}H_{18}O_3$ $(M)^+$ calcd 234.1256, measured 234.1260.

2,2-Dimethylpropionic acid 5-formyl-2-methoxy-4-methylphenyl ester (3e)

Isolated in 23% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ10.13 (s, 1H), 7.48 (s, 1H), 7.78 (s, 1H), 3.89 (s, 3H), 2.68 (s, 3H), 1.37 (s, 9H).

Trifluoromethanesulfonic acid 5-formyl-2,4-dimethylphenyl ester (7a)

Isolated in 41% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.22 (s, 1H), 7.67 (s, 1H), 7.24 (s, 1H), 2.67 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 146.9, 140.6, 137.2, 135.6, 133.5, 123.4, 118.6 (q, J = 318 Hz), 18.7, 16.7.

Trifluoromethanesulfonic acid 5-formyl-2-methoxy-4-methylphenyl ester (7c)

Isolated in 96% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.25 (s, 1H), 7.69 (s, 1H), 6.89(s, 1H), 4.01 (s, 3H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.4, 155.4, 143.7, 137.2,

127.5, 124.8, 118.8 (q, J = 318 Hz), 115.8, 56.7, 19.3; IR (film) 2870, 1709, 1607; HRMS *m/e* (EI) for $C_{10}H_9F_3O_5S$ $(M)^+$ calcd 298.0123, measured 298.0127.

Trifluoromethanesulfonic acid 4-bromo-5-formyl-2-methoxyphenyl ester (7g)

Isolated in 47% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 7.80 (s, 1H), 7.28 (s, 1H), 4.04 (s, 3H).

Trifluoromethanesulfonic acid 5-formyl-2-methoxyphenyl ester (7k)

Isolated in 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.90 (dd, J = 8.8 Hz, J = 2.0 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 4.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3, 156.5, 139.3, 132.2, 130.2, 123.1, 118.9 (q, J = 318 Hz), 113.2, 56.9.

General procedure for the bromination of pivalate and triflate

To a solution of the pivalate or triflate (1.0 equiv.) in acetic acid (0.5 M) was added bromine (1.0 equiv.) at rt. After being stirred for 12 h at rt, the mixture was diluted with CH_2Cl_2, washed with water, dried over $MgSO_4$, concentrated in vacuum and purified by a flash column chromatography to afford the bromide.

2,2-Dimethylpropionic acid 5-bromo-2,4-dimethylphenyl ester (3b)

Isolated in 64% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 1H), 7.09 (s, 1H), 2.35 (s, 3H), 2.09 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 148.0, 135.3, 132.9, 129.5, 125.6, 121.5, 39.4, 27.4, 22.3, 15.9; HRMS *m/e* (EI) for $C_{13}H_{17}BrO_2$ $(M)^+$ calcd 284.0412, measured 284.0416.

2,2-Dimethylpropionic acid 2-bromo-4-methylphenyl ester (4h)

Isolated in 30% yield. Identical to compound **2c** by ^{1}H NMR.

Trifluoromethanesulfonic acid 5-bromo-2-methoxy-4-methylphenyl ester (7d)

Isolated in 100% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 6.92 (s, 1H), 3.90 (s, 3H), 2.41 (s, 3H).

Trifluoromethanesulfonic acid 4,5-dibromo-2-methoxyphenyl ester (7h)

Isolated in 97% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.30 (s, 1H), 3.93 (s, 3H).

2,2-Dimethylpropionic acid 2-bromo-5-(2,2-dimethylproionyloxy)-phenyl ester (10a)

Isolated in 92% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 8.7 Hz, 1H), 6.93 (d, J = 2.4 Hz, 1H), 6.88 (dd, J = 8.7 Hz, J = 2.4 Hz, 1H), 1.40 (s, 9H), 1.35 (s, 9H).

2,2-Dimethylpropionic acid 6-bromo-3-(2,2-dimethylpropionyloxy)-2-methylphenyl ester (10b)

Isolated in 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.7 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 1H), 2.0 (s, 3H), 1.43 (s, 9H), 1.38 (s, 9H).

General procedure for the alkylation of pivalate and triflate

To a suspension of $AlCl_3$ (1.2 equiv.) in $ClCH_2CH_2Cl$ (0.1 M) was added 2-bromopropane (1.2 equiv.) at rt under argon. To the resulting mixture was added a solution of the pivalate or triflate (1.0 equiv.) in $ClCH_2CH_2Cl$ (0.6 M) at rt under argon. The reaction was stirred for 18 h. The resulting mixture was poured into ice water, extracted with CH_2Cl_2, dried over $MgSO_4$, concentrated in vacuum and purified by a flash column chromatography to afford a product.

Trifluoromethanesulfonic acid 5-isopropyl-2-methoxy-4-methylphenyl ester (7e)

Isolated in 51% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (s, 1H), 6.80(s, 1H), 3.88 (s, 3H), 3.13-3.00 (m, 1H), 2.35 (s, 3H), 1.19 (d, J = 6.9 Hz, 6H).

Demethylated byproduct -Trifluoromethanesulfonic acid 2-hydroxy-5-isopropyl-4-methylphenyl ester (7e[a])

Isolated in 42% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (s, 1H), 6.83(s, 1H), 3.12-2.98 (m, 1H), 2.28 (s, 3H), 1.19 (d, J = 6.9 Hz, 6H).

Trifluoromethanesulfonic acid 4-bromo-5-isopropyl-2-methoxyphenyl ester (7i)

Isolated in 42% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1H), 7.10 (s, 1H), 3.90 (s, 3H), 3.33-3.24 (m, 1H), 1.22 (d, *J* = 7.2 Hz, 6H).

Demethylated byproduct -Trifluoromethanesulfonic acid 4-bromo-2-hydroxy-5-isopropylphenyl ester (7i^b)

Isolated in 56% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (s, 1H), 7.11 (s, 1H), 5.61 (s. 1H), 3.33-3.23 (m, 1H), 1.22 (d, *J* = 6.8 Hz, 6H).

General procedure for the acylation reaction of pivalate and triflate

To a suspension of $AlCl_3$ (1.1 equiv.) in $ClCH_2CH_2Cl$ (0.1 M) was added acetyl chloride (1.0 equiv.) at rt under argon. To the resulting mixture was added a solution of the pivalate or triflate (1.0 equiv.) in $ClCH_2CH_2Cl$ (0.2 M) at rt under argon. The reaction was stirred for 1 day. The resulting mixture was poured into ice water, extracted with CH_2Cl_2, dried over $MgSO_4$, concentrated in vacuum and purified by a flash column chromatography to afford the ketone.

Trifluoromethanesulfonic acid 5-acetyl-2-methoxy-4-methylphenyl ester (7f)

Isolated in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 1H), 6.88(s, 1H), 3.97 (s, 3H), 2.61 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 153.6, 142.5, 135.9, 129.7, 124.7, 119.0 (q, J = 318 Hz), 116.5, 56.6, 29.3, 22.7.

Trifluoromethanesulfonic acid 5-acetyl-4-bromo-2-methoxyphenyl ester (7j)

Isolated in 29% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.28 (s, 1H), 3.98 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 153.5, 137.5, 133.0, 124.3, 120.7, 118.8, 118.7 (q, J = 318 Hz), 56.9, 30.0.

Trifluoromethanesulfonic acid 5-acetyl-2-methoxyphenyl ester (7l)

Isolated in 94% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, J = 8.7 Hz, J = 2.1 Hz, 1H), 7.84 (d, J = 2.1 Hz, 1H), 7.09 (d, J = 8.7 Hz, 1H), 4.00 (s, 3H), 2.57(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2, 155.4, 138.8, 130.8, 130.3, 122.8, 118.9 (q, J = 318 Hz), 112.6, 56.8, 26.4.

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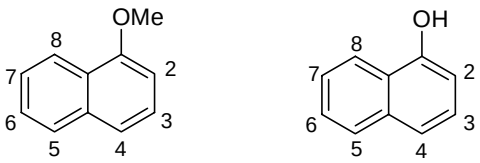
Chapter 2. Regioselective functionalizations of 1-methoxynaphthalene and α-naphthol

Introduction



1-Methoxynaphthalene and α-naphthol are readily available compounds which serve as starting materials for many biologically active natural products.[1] Therefore, efficient ways to functionalize 1-methoxynaphthalene (or α-naphthol) with a controlled regioselectivity are needed.

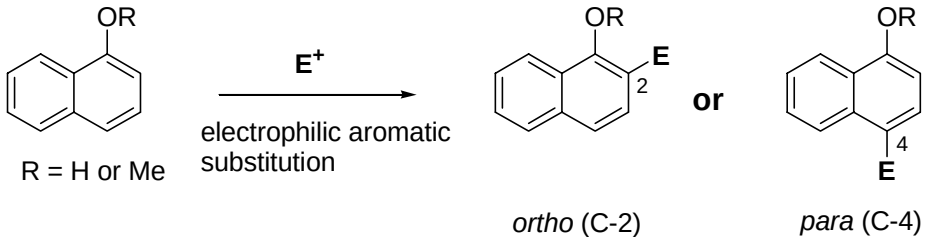


Figure 1

Electrophilic aromatic substitutions of 1-methoxynaphthalene (or α-naphthol) could provide 2-substituted or 4-substituted 1-methoxynaphthalenes (or α-naphthols) since the methoxy or hydroxyl group directs electrophilic aromatic substitutions to the C-2 (*ortho*) and C-4 (*para*) positions (Figure 1).[2] Therefore, many substitution reactions of 1-methoxynaphthalene (or α-naphthol) provided the 2- or 4-substituted 1-methoxynaphthalenes (or α-naphthols) with various kinds of functional groups. Compared to 2- and 4-substituted

1-methoxynaphthalenes (or α-naphthols), 1-methoxynaphthalenes (or α-naphthols) substituted at other positions (C-3, C-5, C-6, C-7 and C-8) are not readily accessible from electrophilic aromatic substitutions.

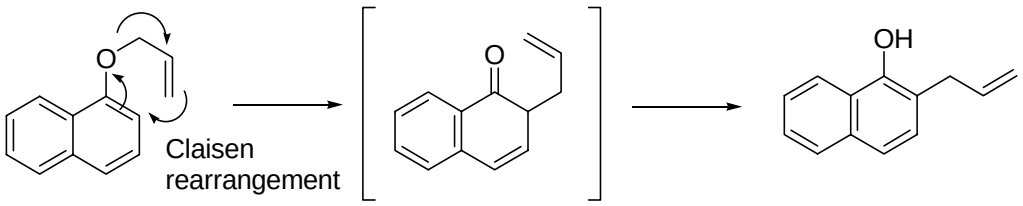


Figure 2

Aromatic Claisen rearrangement has been a powerful carbon-carbon bond forming reaction on arenes.[3] However, the Claisen rearrangement could generate only *ortho*-allyl arenes. Therefore, the Claisen rearrangement of 1-allyloxynaphthalene could give 2-allyl-1-naphthol in a concerted fashion (Figure 2).[4]

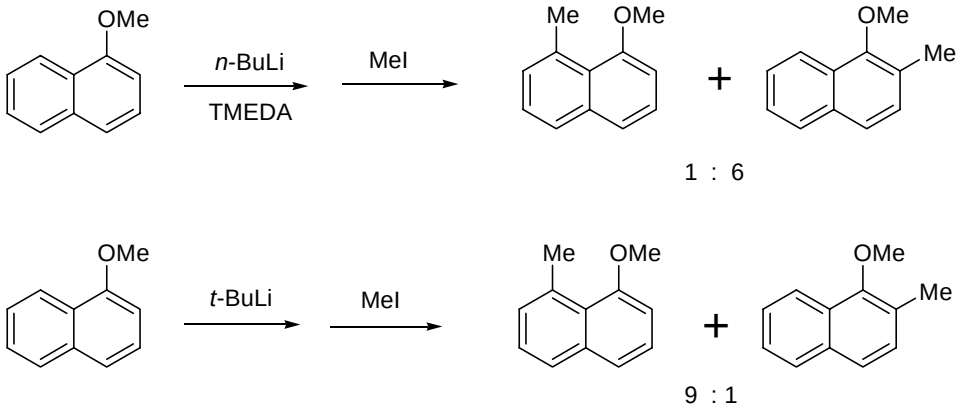


Figure 3

Directed lithiation of 1-methoxynaphthalene was reported to give 2-substituted and 8-substituted 1-methoxynaphthalenes.[5] In the literature, Barnes reported that 1-methoxy-2-methylnaphthalene could be preferentially formed over 1-methoxy-8-methylnaphthalene if *n*-

BuLi with TMEDA was used. In contrast, the use of *t*-BuLi could generate 1-methoxy-8-methylnaphthalene as a major product and 1-methoxy-2-methylnaphthalene as a minor product in the ratio of 9:1 (Figure 3).

Even though there are a wealth of procedures for the synthesis of 2- or 4-substituted 1-methoxynaphthalenes (or α-naphthols), there are only limited examples for the synthesis of 6- or 8-substituted 1-methoxynaphthalene (or α-naphthols).[6] Hence, we studied a novel method to generate 6- and 8-substituted 1-methoxynaphthalenes (or α-naphthols).

Results and Discussion

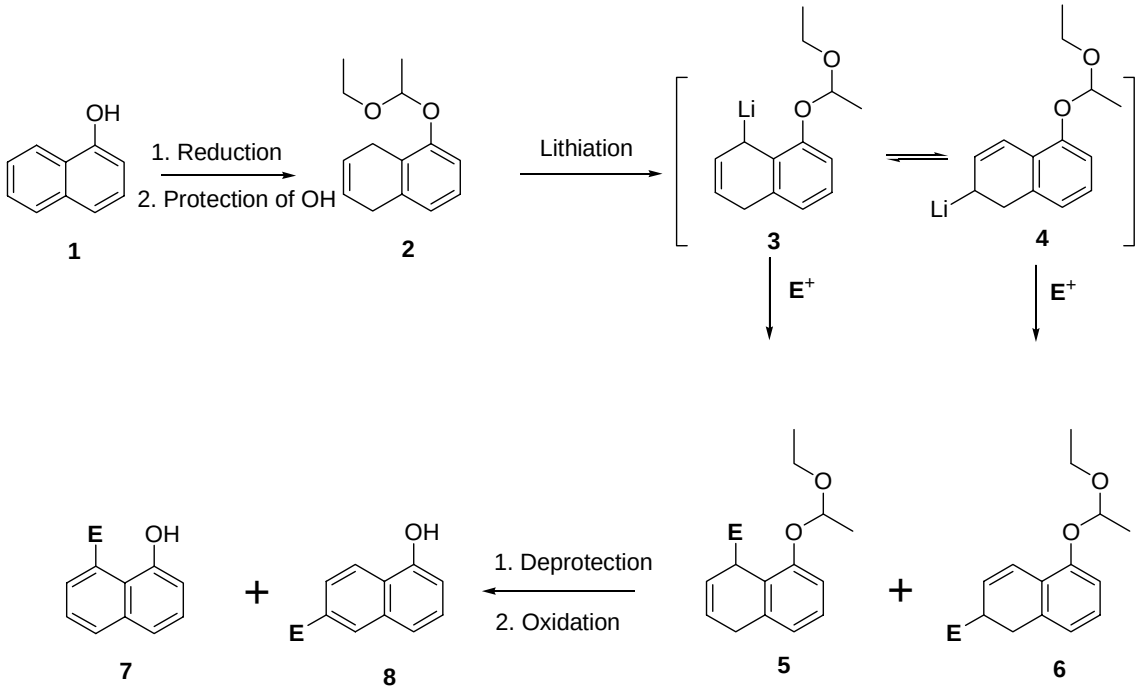


Figure 4

The strategy to synthesize 6-substituted or 8-substituted α-naphthols is depicted in Figure 4. Naphthalene **2** was chosen as a candidate for deprotonation. The Birch reduction[7] of α-naphthol and the protection of the hydroxyl group with ethyl vinyl ether provided

dihydronaphthalene **2**. Treating compound **2** with bases (*n*-BuLi, *tert*-BuLi or *sec*-BuLi) could generate the anion. The anion could react with various electrophiles to provide compounds **5** and **6**. We could then oxidize compounds **5** and **6** to 6- or 8-substituted α-naphthols **7** and **8**.

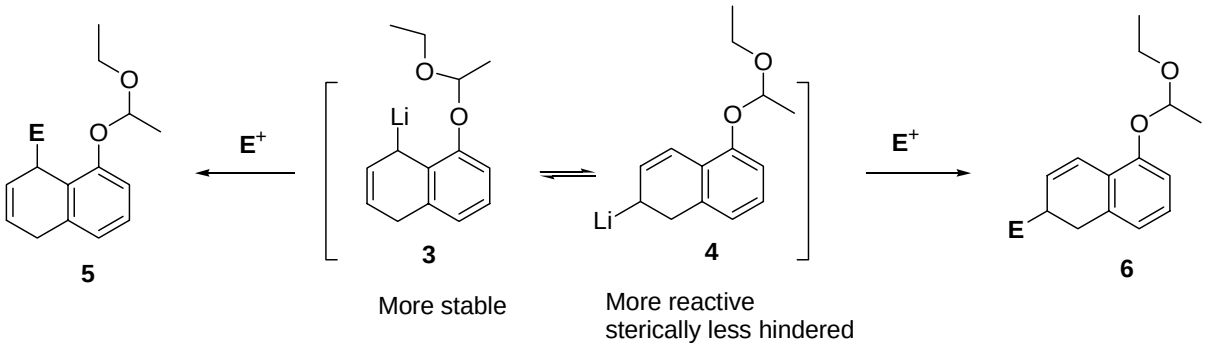
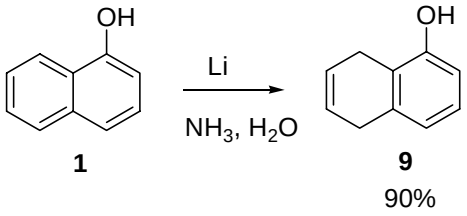


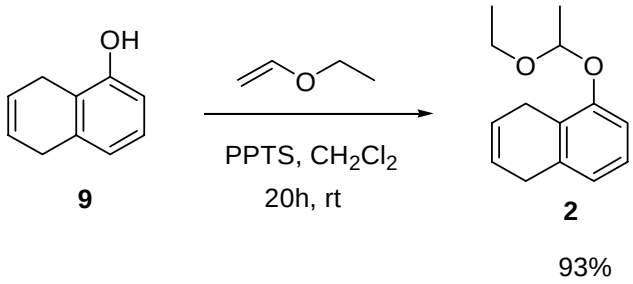
Figure 5

The anion could react with electrophiles to provide 6- or 8-substituted compounds (Figure 5).



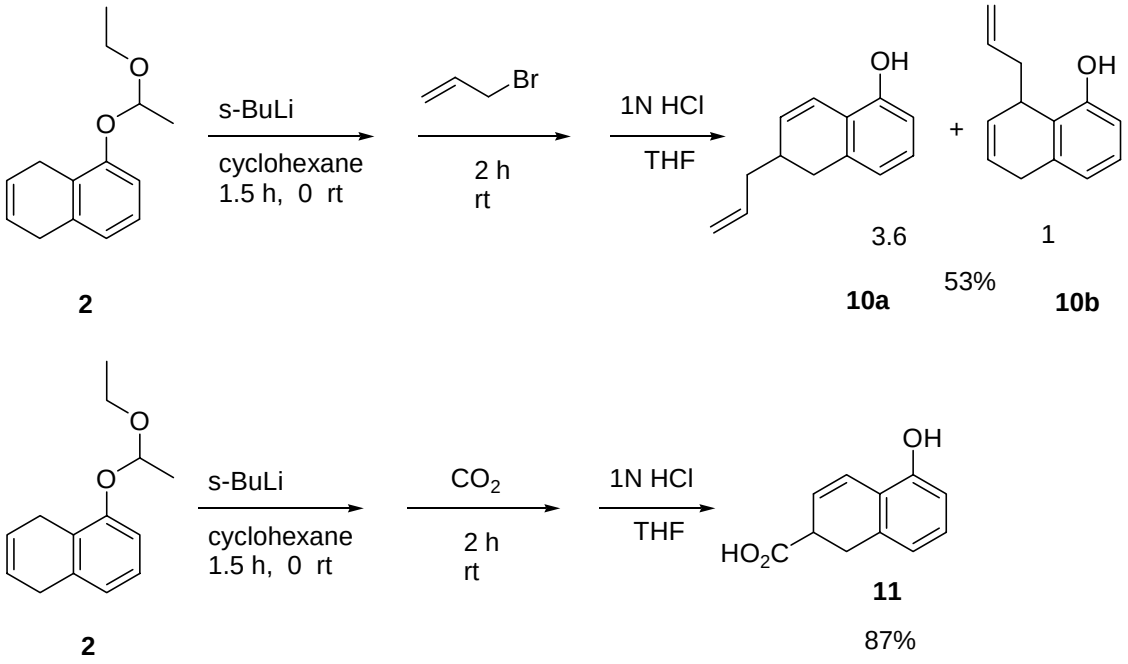
Scheme 1

In 1991, Suzuki reported that Birch reduction of α-naphthol (**1**) provided 5,8-dihydronaphthol (**9**) in 90% yield.[8] We generated 5,8-dihydronaphthol (**9**) in 90% yield by Suzuki's procedure.



Scheme 2

With compound **9** in hand, we protected alcohol **9** with ethyl vinyl ether in the presence of pyridinium *p*-toluenesulfonate (PPTS) as a catalyst. The reaction smoothly provided compound **2** in 93% yield. Several alkyl lithium bases (*n*-BuLi, *tert*-BuLi and *sec*-BuLi) were tested in various solvents (THF, Et_2O and cyclohexane) to find the optimal condition. Among those bases, *sec*-BuLi gave the best result.



Scheme 3

The reactions were carried out with *sec*-BuLi in cyclohexane. Various electrophiles

(allyl bromide, carbon dioxide, benzaldehyde, iodomethane and benzyl bromide) were investigated.[9] The reaction with allyl bromide gave 6-allyl substituted product **10a** and 8-allyl product **10b** in 53% yield in the ratio of 3.6:1. The reaction with carbon dioxide provided 6-substituted compound **11** in 87% yield. Both reactions gave preferentially 6-substituted adducts over 8-substitued adducts (Scheme 3).

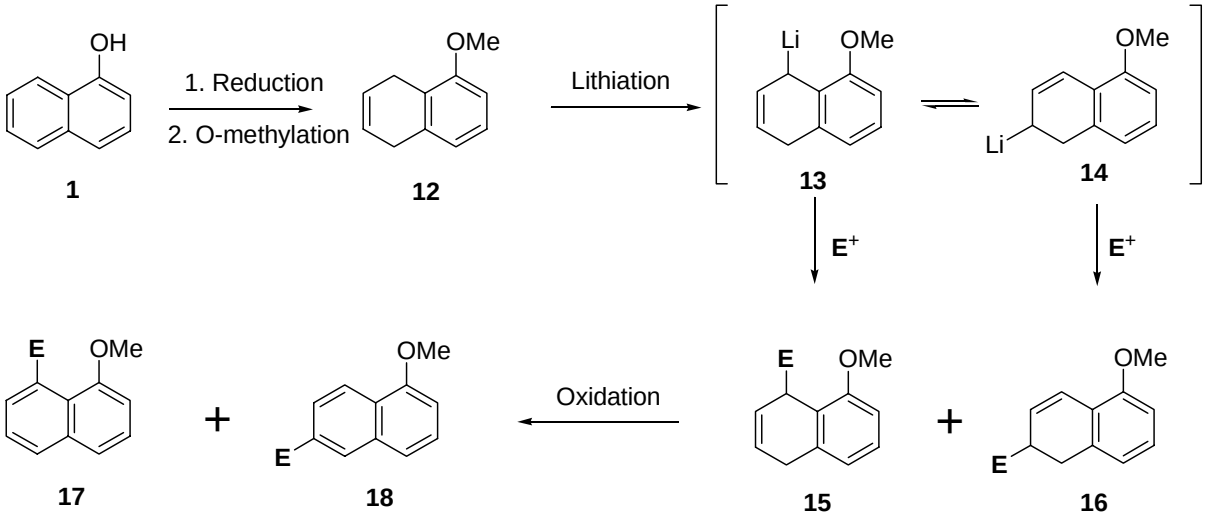
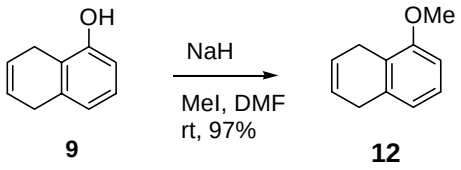


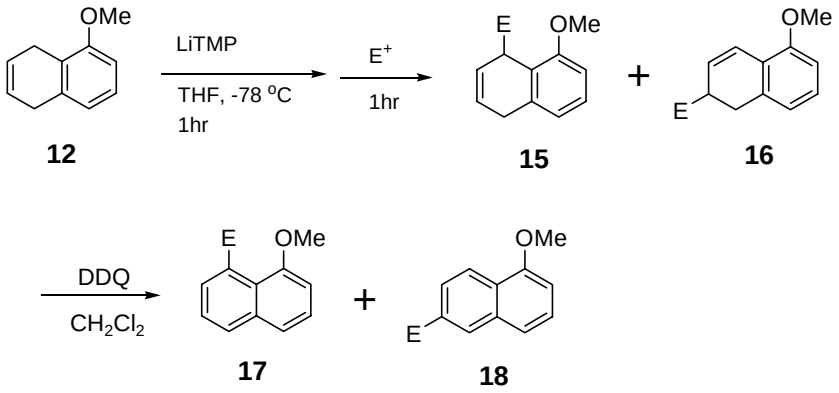
Figure 6

The strategy of synthesizing 6- or 8-substituted 1-methoxynaphthalenes is shown in Figure 6. We could lithiate 1-methoxy-5,8-dihydro-naphthalene (**12**) with a base. The lithiated 5,8-dihydro-naphthalene could react with electrophiles to provide compounds **15** and **16**. Finally, we could oxidize compounds **15** and **16** to provide 6- or 8-substituted 1-methoxynaphthalenes.



Scheme 4

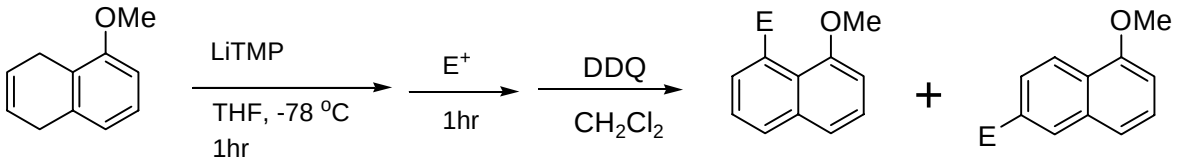
Compared to dihydronaphthalene **2**, dihydronaphthalene **12** is more stable. Moreover, the methoxy group of compound **12** did not contain a stereogenic center. The lithiation reactions of 1-methoxy-5,8-dihydronaphthalene (**12**) were screened with various bases (*n*-BuLi, *tert*-BuLi, *sec*-BuLi and LiTMP) and solvents (THF, Et_2O and cyclohexane).



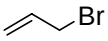
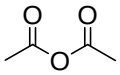
Scheme 5

The best conditions of the lithiation reaction involved lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in THF. Therefore, 1-methoxy-5,8-dihydronaphthalene (**12**) was lithiated with LiTMP in THF and several electrophiles (allyl bromide, carbon dioxide, acetic anhydride and ethylene oxide) were added. The oxidation of the products with 2,3-dicyano-5,6-dichloro-*p*-benzoquinone (DDQ) smoothly provided 6- or 8-substituted 1-methoxynaphthalenes.

Table 1. Synthesis of 6- or 8-substituted 1-methoxynaphthalenes



12 **17** **18**

Entry	$\mathbf{E}^+$	% yield of **17**	% yield of **18**
a		67(**17a**)	-
b	CO_2	75*(**17b**)	-
c		43(**17c**)	12(**18c**)
d		52(**17d**)	40(**18d**)

* We were not able to purify the carboxylic acid by a flash column chromatography. Hence, we methylated carboxylic acid to methyl ester which we could purify by a flash column chromatography.

The results of the reactions are shown in Table 1. Interestingly, the anion from 1-methoxy-5,8-dihydronaphthalene (**12**) preferentially gave 8-substituted dihydronaphthalenes as the major or only product. The structures of compounds **17** and **18** were determined by proton NMR. The 6-substituted 1-methoxy-naphthalenes showed a singlet aromatic proton signal from C-5.

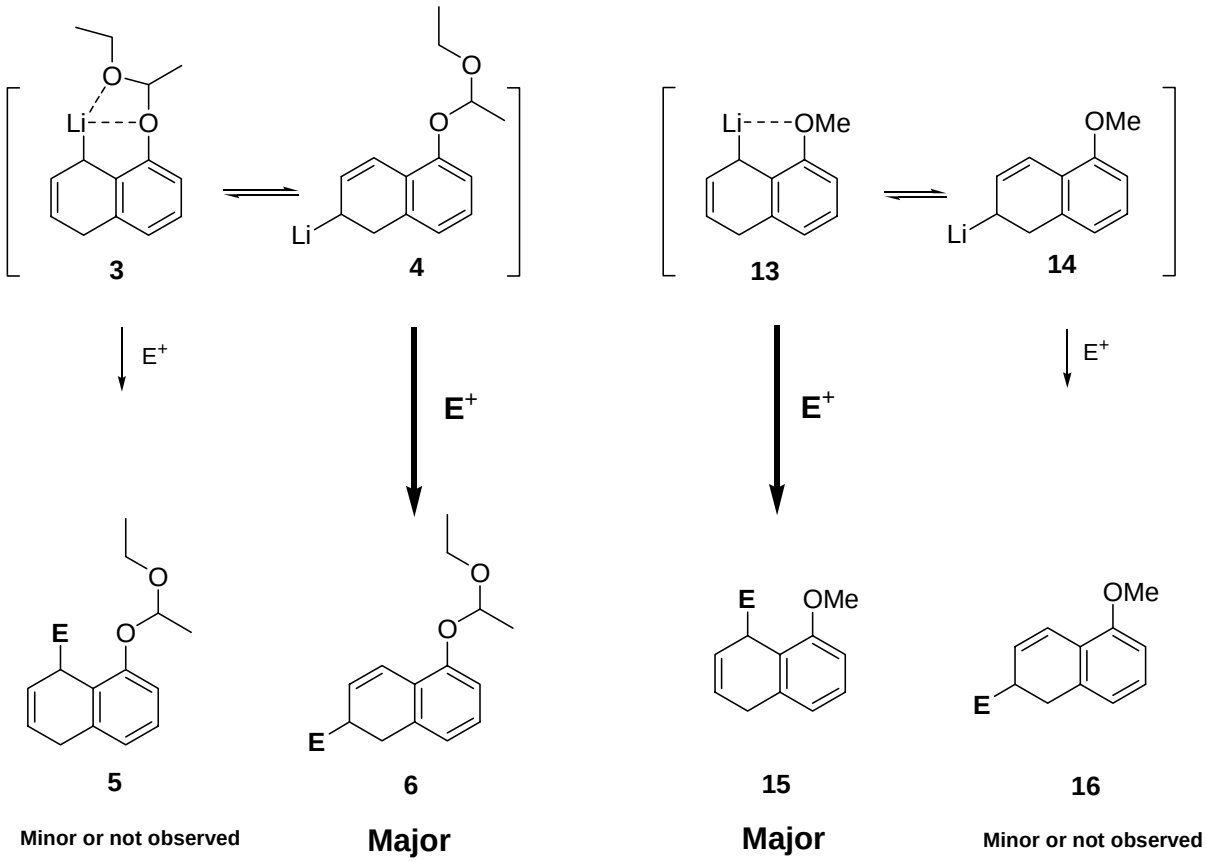


Figure 7

We reasoned that the methoxy group of 1-methoxy-5,8-dihydronaphthalene (**12**) afforded less steric hinderance than the 1-ethoxyethoxy group of dihydronaphthalene **2** to provide dihydronaphthalene **15** as the major product (Figure 7).

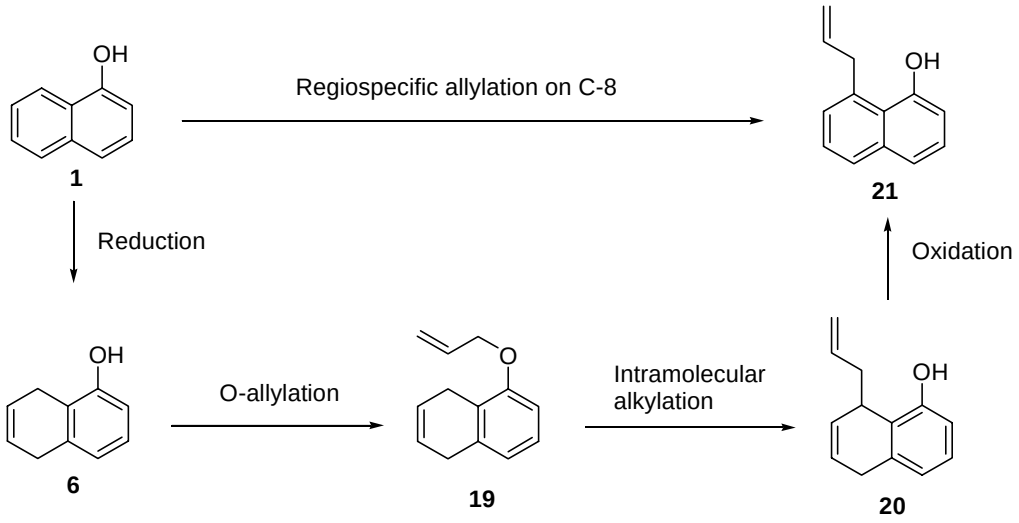


Figure 8

The intramolecular alkylation of 1-allyloxy-5,8-dihydronaphthalene (**19**) was also studied (Figure 8). The allyl group was selected as a protecting group and as a plausible electrophile.

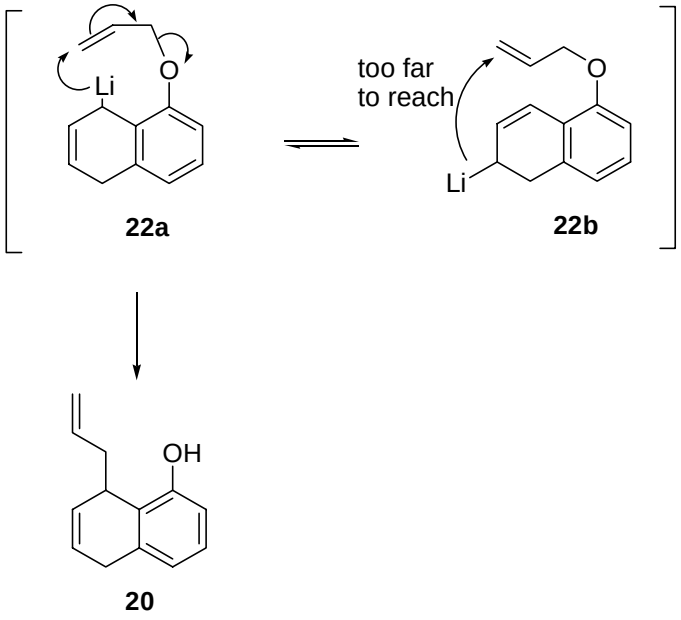
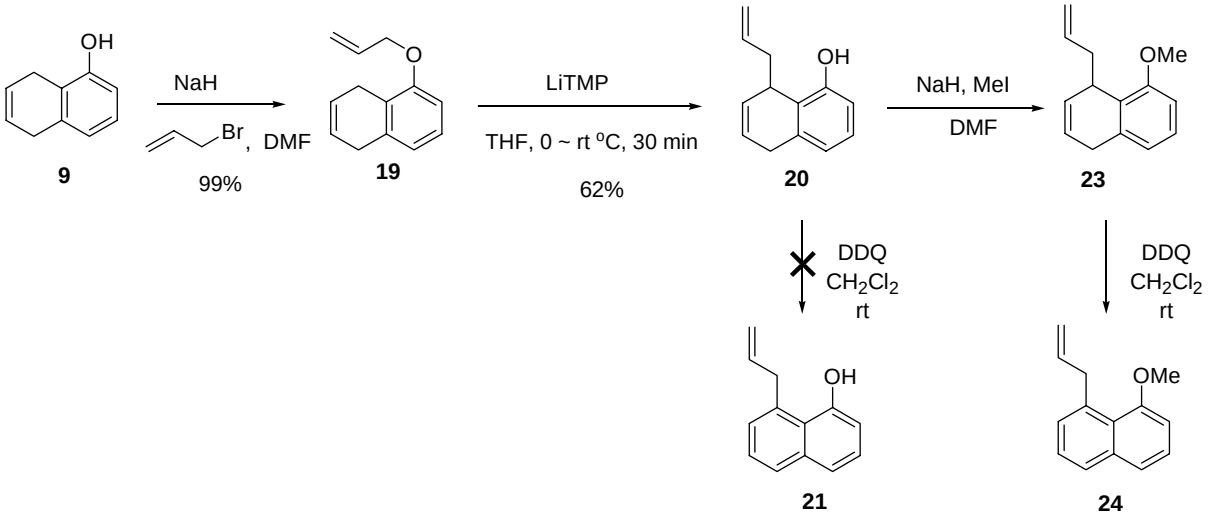


Figure 9

The intramolecular allylation of 1-allyloxy-5,8-dihydronaphthalene (**19**) should give 8-

allyl-5,8-dihydro-1-naphthol (**20**) as the only product (Figure 9).



9 **19** **20** **23** **21** **24**

Scheme 6

The protection of 5,8-dihydro-1-naphthol (**6**) with allyl bromide[10] formed 1-allyloxy-5,8-dihydronaphthalene (**19**) in 99% yield. With compound **19** in hand, we tested several bases (*n*-BuLi, *tert*-BuLi, *sec*-BuLi and LiTMP) and solvents (THF, Et_2O and cyclohexane) to find the best conditions for the intramolecular allylation (Scheme 6). We achieved the best yield with LiTMP in THF. The reaction gave 8-allyl-5,8-dihydro-1-naphthalenol (**20**) as the only product as expected. We tried to the oxidation of compound **16** with DDQ. However, the oxidation did not provide 8-allyl-1-naphthol (**21**). After protecting compound **20** with sodium hydride and methyl iodide, we could oxidize compound **23** to 1-methoxy-8-allyl-naphthalene (**24**) which was identical to compound **17a** in Table 1. In conclusion, we successfully developed a novel methodology to provide 6- or 8-substituted 1-methoxy-naphthalenes (or α-naphthols). The intramolecular alkylation of 1-allyloxynaphthalene gave 8-allyl-1-naphthol as the only product.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane and benzene were distilled over calcium hydride. All experiments were performed under argon atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.27 ppm for ^1H and 77.23 ppm for ^{13}C), unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 A, 32-63 μm) was used for a flash column chromatography.

1-(1-Ethoxy-ethoxy)-5,8-dihydronaphthalene (2)

To a solution of compound **6** (3.3g, 22 mmol) in CH_2Cl_2 (80 mL) was added PPTS (11mg, 0.22 mmol) followed by ethyl vinyl ether (3.2 mL, 34 mmol) at rt under argon. After being stirred at room temperature for 12 h, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, concentrated in vacuum and purified by column chromatography to afford compound **2** (4.5 g, 20 mmol) in 93% yield. ^1H NMR (400 MHz, $CDCl_3$) δ7.10 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 5.98-5.75 (m, 2H), 5.41 (q, *J* = 5.2 Hz, 1H), 3.83-3.75 (m, 1H), 3.59-3.48 (m, 1H), 3.41 (s, 2H), 3.32 (s, 2H), 1.52 (d, *J* = 5.2, 3H), 1.22 (t, *J* = 6.8, 3H).

6-Allyl-5,6-dihydronaphthalen-1-ol (10a) and 8-allyl-5,8-dihydronaphthalen-1-ol (10b)

To a solution of compound **2** (86 mg, 0.40 mmol) in cyclohexane (5 mL) at 0 ^{o}C under argon was slowly added *s*-BuLi (1M solution in hexane, 0.44 mL, 0.44 mmol). After being stirred at room temperature for 1.5 h, allyl bromide (50 μL, 0.59 mmol) was added to the reaction mixture then, stirred for 2 h at rt. The reaction mixture was diluted with EtOAc, washed with water, dried over $MgSO_4$ and concentrated in vacuum. The crude residue was stirred with 1N aqueous HCl (1 mL) in THF (5 mL) at rt for 6h. The solution was diluted with EtOAc, washed with water, dried over $MgSO_4$, concentrated in vacuum and purified by column chromatography to afford **10a** (31 mg) in 41% yield and **10b** (9 mg) in 12 % yield. **Compound 10a**; ^{1}H NMR (400 MHz, $CDCl_3$) δ6.99 (t, *J* = 8 Hz, 1H), 6.77-6.69 (m, 2H), 6.61 (d, *J* = 8 Hz, 1H), 6.01-5.94 (m, 1H), 5.89-5.75 (m, 1H), 5.03-5.12 (m, 2H), 4.66 (s, 1H), 2.86-2.79 (m, 1H), 2.64-2.45 (m, 2H), 2.12-2.29 (m, 2H). **Compound 10b**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (t, *J* = 7.8 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 6.06-5.94 (m, 2H), 5.91-5.76 (m, 1H), 5.10-4.98 (m, 2H), 4.84 (s, 1H), 3.79-3.68 (m, 1H), 3.48-3.25 (m, 2H), 2.60-2.49 (m, 1H), 2.47-2.35 (m, 1H).

5-Hydroxy-1,2-dihydro-naphthalene-2-carboxylic acid (11)

To a solution of compound **2** (86 mg, 0.40 mmol) in cyclohexane (5 mL) at 0 ^{o}C under argon was slowly added *s*-BuLi (1M solution in hexane, 0.44 mL, 0.44 mmol). After being stirred at room temperature for 1.5 h, CO_2 was bubbled to the reaction mixture then, stirred for 2 h at rt. The reaction mixture was diluted with EtOAc, washed with water, dried over $MgSO_4$ and concentrated in vacuum. The crude residue was stirred with 1N aqueous HCl (1

mL) in THF (5 mL) at rt for 6 h. The solution was diluted with EtOAc, washed with water, dried over $MgSO_4$, concentrated in vacuum and purified by column chromatography to afford compound **11** (66 mg, 0.35 mmol) in 87 % yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ7.04 (t, *J* = 7.8 Hz, 1H), 6.91 (dd, *J* = 9.9 Hz, *J* = 1.8 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 6.12 (dd, *J* = 9.9 Hz, *J* = 3.6 Hz, 1H), 3.54-3.44 (m, 1H), 3.01-3.18 (m, 2H).

1-Methoxy-5,8-dihydronaphthalene (12)

To a suspension of NaH (1.58 g, 39.5 mmol) in DMF (50 mL) was slowly added alcohol **9** (4.74 g, 32.9 mmol) under argon at rt. The mixture was stirred for 1 h at rt. To the resulting mixture was added MeI (7.01 g, 49.4 mmol) at rt. After being stirred for 12 h, the mixture was poured into water, diluted with Et_2O, washed with water several times, dried over $MgSO_4$, concentrated in vacuum and purified by a flash column chromatography to afford compound **12** (5.11 g, 31.9 mmol) in 97% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ7.14 (t, *J* = 7.8 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 5.99-5.82 (m, 2H), 3.83 (s, 3H), 3.45-3.38 (m, 2H), 3.31-3.24 (m, 2H).

General procedure for the synthesis of 6-or 8- substituted 1-methoxynaphthalene

To a solution of 2,2,6,6-tetramethylpiperidine (1.2 equiv.) in THF (0.1 M) was added *n*-BuLi (1.2 equiv., 2.5 M in hexane) at rt under argon. After being stirred for 30 min at 0 ^{o}C, a solution of compound **12** (1 equiv.) in THF (0.2 M) was added to the reaction mixture at -78 ^{o}C. The resulting mixture was stirred at -78 ^{o}C under argon. After being stirred for 1h at -78 ^{o}C, electrophile (1.5 equiv.) was added to the reaction mixture. The reaction mixture was stirred for 1 h while allowing it to warm to rt. The mixture was diluted with Et_2O,

washed with brine, dried over $MgSO_4$ and concentrated in vacuum to afford a crude residue. To a crude residue in CH_2Cl_2 (0.1 M) was added DDQ (1.1 equiv.) at rt. After being stirred for 3 h at rt, the reaction mixture was filtered, concentrated in vacuum and purified by a flash column chromatography to afford 6- or 8-substituted 1-methoxynaphthalene.

1-Allyl-8-methoxynaphthalene (17a)

Isolated in 67% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.69 (d, *J* = 8 Hz, 1H), 7.45 (d, *J* = 8 Hz, 1H), 7.41-7.35 (m, 2H), 7.27 (d, *J* = 6.8 Hz, 1H), 6.86 (d, *J* = 7.2 Hz, 1H), 6.26-6.13 (m, 1H), 5.06-5.00 (m, 2H), 4.11 (d, J = 6 Hz, 2H), 3.96 (s, 3H)

8-Methoxynaphthalene-1-carboxylic acid methyl ester (17b)

Isolated in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.87 (dd, *J* = 8 Hz, *J* = 1.6 Hz, 1H), 7.50-7.42 (m, 4H), 6.90 (dd, *J* = 7.2 Hz, *J* = 1.2 Hz, 1H), 3.98 (s, 3H), 3.97 (s, 3H)

1-(8-Methoxy-naphthalen-1-yl)ethanone (17c)

Isolated in 43% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.84 (dd, *j* = 0.8 Hz, *j* = 8 Hz, 1H), 7.51-7.42 (m, 3H), 7.24 (dd, *j* = 0.8 Hz, *j* = 7.2 Hz, 1H), 6.89 (dd, *j* = 0.8 Hz, *j* = 7.2 Hz, 1H), 3.95 (s, 3H), 2.53 (s, 3H)

1-(5-Methoxy-naphthalen-2-yl)ethanone (18c)

Isolated in 12% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ8.43 (d, *J* = 1.2 Hz, 1H), 8.32 (d, *J* = 8.8 Hz, 1H), 8.02 (dd, *J* = 8.8 Hz, *J* = 1.6 Hz, 1H), 7.55 (d, *J* = 8 Hz, 1H), 7.47 (t, *J* = 8 Hz, 1H), 6.94 (d, *J* = 8 Hz, 1H), 4.04 (s, 3H), 2.74 (s, 3H).

2-(8-Methoxy-naphthalen-1-yl)ethanol (17d)

Isolated in 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.70 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 8 Hz, 1H), 7.40-7.35 (m, 2H), 7.28 (d, *j* = 7.6 Hz, 1H), 7.87 (d, *J* = 7.6Hz, 1H), 3.98-3.95 (m, 5H), 3.58 (t, *J* = 6.4 Hz, 3H).

2-(5-Methoxy-naphthalen-2-yl)ethanol (18d)

Isolated in 40% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ8.23 (dd, *J* = 7.4 Hz, *J* = 2.4 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.46-7.41 (m, 3H), 6.85 (d, *J* = 7.6 Hz, 1H), 4.02-3.98 (m, 5H), 3.35 (t, *J* = 6.4 Hz, 3H)

1- Allyloxy-5,8-dihydronaphthalene (19)

To a suspension of NaH (0.38 g, 9.65 mmol) in DMF (10 mL) was added alcohol **9** (1.16 g, 8.04 mmol) at rt under argon. The resulting mixture was stirred for 1 h at rt. To the mixture was added allyl bromide (1.45 g, 12.1 mmol). After being stirred for 6 h, the mixture was poured into water, diluted with Et_2O, washed with water several times, dried over $MgSO_4$, concentrated in vacuum and purified by a flash column chromatography to afford compound **19** (1.48 g, 7.95 mmol) in 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.11 (t, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 6.13-6.03 (m, 1H), 5.96-5.85 (m, 2H), 4.44 (dd, *J* = 17.2 Hz, *J* = 1.6 Hz, 1H), 2.28 (dd, *J* = 10.8 Hz, *J* = 1.6 Hz, 1H), 4.58-4.52 (m, 2H), 3.46-3.40 (m, 2H), 3.37-3.30 (m, 2H).

8-allyl-5,8-dihydronaphthalen-1-ol (20)

To a solution of 2,2,6,6-tetramethyl piperidine (0.23 mL, 1.34 mmol) in THF (0.1 M) was

added n-butyl lithium (0.61 mL, 2.2 M in hexane, 1.34 mmol) at 0 ^{o}C under argon. After being stirred for 30 min, compound **19** (0.21 g, 1.12 mmol) was dropwise added to the mixture at 0 ^{o}C and the reaction mixture was stirred for 30 min at rt. The reaction mixture was quenched with water (1 mL), diluted with ethyl acetate, washed with brine, dried over $MgSO_4$, concentrated in vacuum and purified by a flash column chromatography to afford compound **20** (0.13 g, 0.69 mmol) in 62 % yield which was identical to compound **10b** by ^{1}H NMR.

1-Allyl-8-methoxy-1,4-dihydronaphthalene (23)

To a suspension of NaH (5 mg, 0.114 mmol) in DMF (3 mL) was added alcohol **20** (19 mg, 0.10 mmol) at rt under argon. The resulting mixture was stirred for 30 min at rt. To the mixture was added MeI (22 mg, 0.15 mmol). After being stirred for 12 h, the mixture was poured into water, diluted with Et_2O, washed with water several times, dried over $MgSO_4$, concentrated in vacuum and purified by a flash column chromatography to afford compound **23** (20 mg, 0.10 mmol) in 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.15 (t, *J* = 8.0 Hz, 1H), 6.76-6.72 (m, 2H), 5.96 (d, *J* = 1.6 Hz, 2H), 5.86-5.71 (m, 1H), 5.00-4.91 (m, 2H), 3.85 (s, 3H), 3.79-3.70 (m, 1H), 3.45-3.23 (m, 2H), 2.54-2.46 (m, 1H), 2.37-2.29 (m, 1H).

1-Allyl-8-methoxynaphthalene (24)

To a solution of compound **23** (25 mg, 0.13 mmol) in CH_2Cl_2 (5 mL) was added DDQ (32 mg, 0.14 mmol) ar rt. After being stirred for 3 h, the mixture was filtered, concentrated in vacuum and purified by a flash column chromatography to afford compound **24** (25 mg,

0.126 mmol) in 99% yield, which was identical to compound **17a** by ^{1}H NMR.

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9. The reactions with benzaldehyde, iodomethane and benzyl bromide seemed to provide alkylated products in crude ^{1}H NMR. However, a conventional flash column chromatography (silica gel) could not purify any product due to very close polarities of the mixtures on silica gel.

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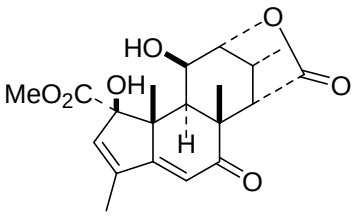
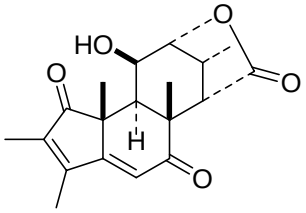
Chapter 3. Synthetic approach to eurycolactone C

Introduction

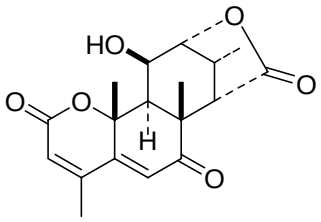
Eurycoma longifolia Jack is a Malaysian plant known for its diverse biological activities, such as antimalarial, antiulcer, antipyretic and cytotoxic activities.[1]



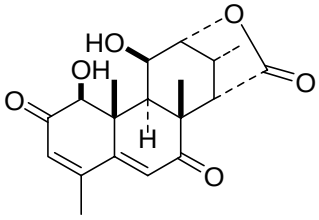
1: Eurycolactone A



2: Eurycolactone B (X = Cl)
5: Laurycolactone B (x = H)



3: Eurycolactone C



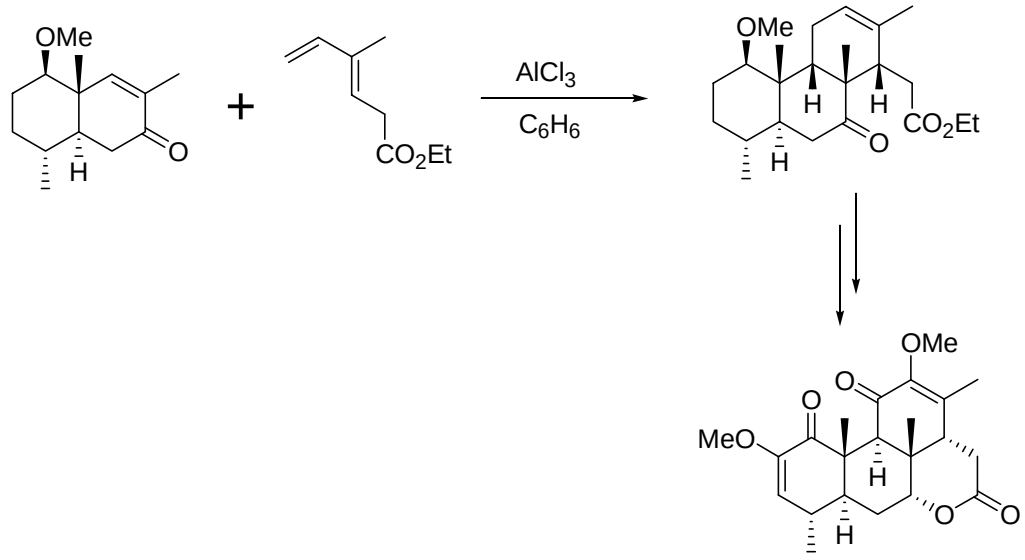
4: 5,6-Dehydroeurycomalactone

Figure 1

From this plant, Takeya and coworkers isolated three novel C_{19} and C_{18} quassinoids, eurycolactones A-C (**1**-**3**), having unique structural features along with several known quassinoids including 5,6-dehydroeurycomalactone (**4**) and laurycolactone B (**5**) and elucidated the structures of these novel quassinoids. Despite their interesting biological activities as well as their unique carbon framework, no synthetic approach towards these compounds had been reported. By contrast to quassinoids from *Eurycoma longifolia Jack*,

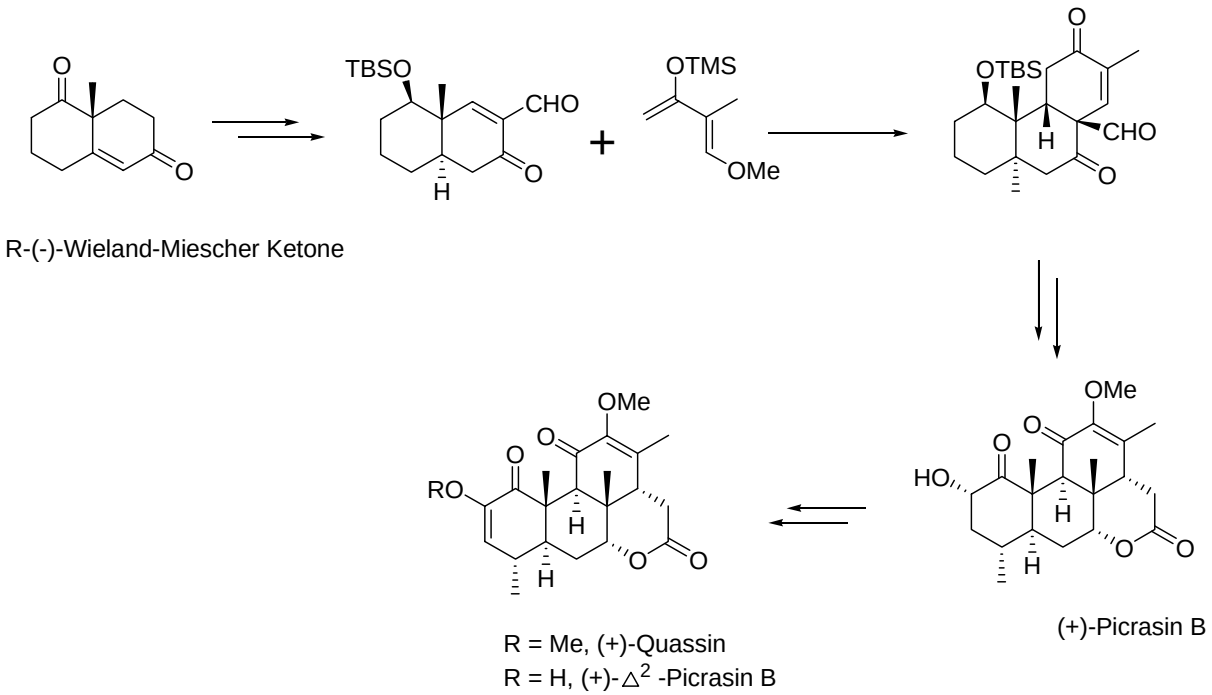
extensive synthetic work[2] has been carried out on other quassinoids[3] such as quassin,[4] castelanolide,[5] klaineanone,[6] quassimarin,[7] bruceantin,[8] samaderin B,[9] shinjulactone C,[10] amarolide,[11] picrasin B[13] and samaderine Y[14].

In 1980, Grieco[12] reported the total synthesis of quassin isolated from *Quassia amara* in 1937. In the synthesis of quassin, he employed the strategy of the intermolecular Diels-Alder reaction catalyzed by aluminum chloride to construct a tricyclic ketone.



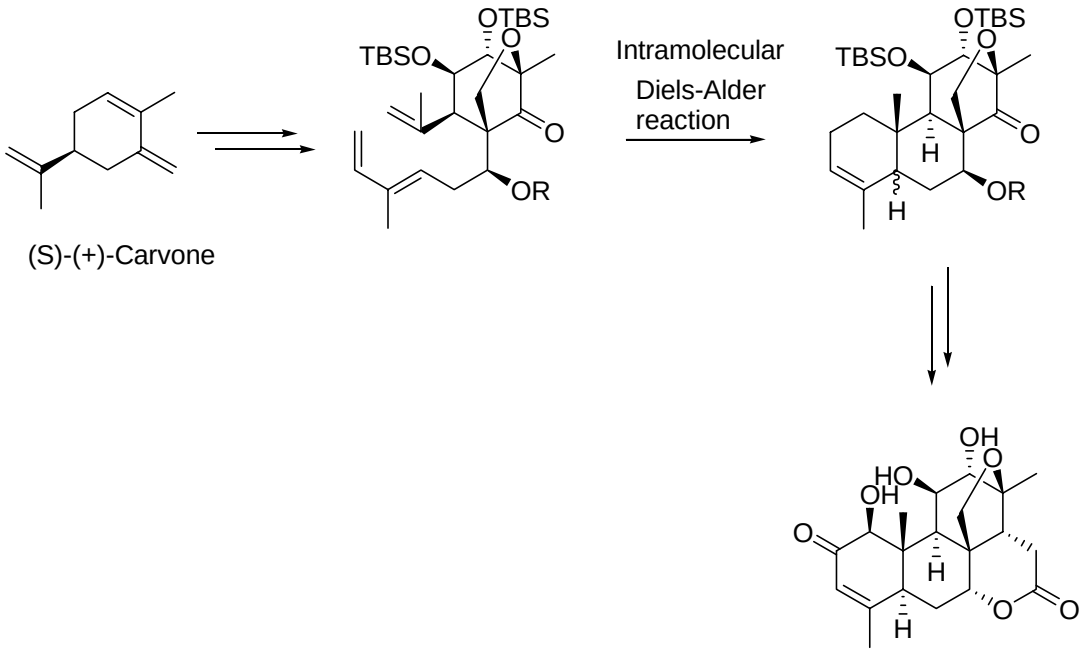
(±)-Quassin

In 1989, Watt[13] and coworkers reported an enantioselective total synthesis of (+)-picrasin B, (+)-Δ^2-picrasin B and (+)-quassin from the R-(-) enantiomer of the Wieland-Miescher ketone. He used an A-AB-ABC-ABCD sequence to assemble the tetracyclic skeleton.



The crucial step in this sequence relied upon a Diels-Alder reaction of a bicyclic dienophile with 1-methoxy-2-methyl-3-((trimethylsilyl)oxy)-1,3-butadiene to obtain a tricyclic skeleton.

In 2005, Shing[14] reported the first total synthesis of (-)-samaderine Y, which has been shown to display in vitro cytotoxicity and is of interest as a potential antitumor agent.



(S)-(+)-Carvone

(-)-Samaderine Y

Its synthesis has been accomplished from (S)-(+)-carvone in 21 steps. In the synthesis of (-)-samaderine Y, they used the intramolecular Diels-Alder reaction as a key step.

Results and Discussion

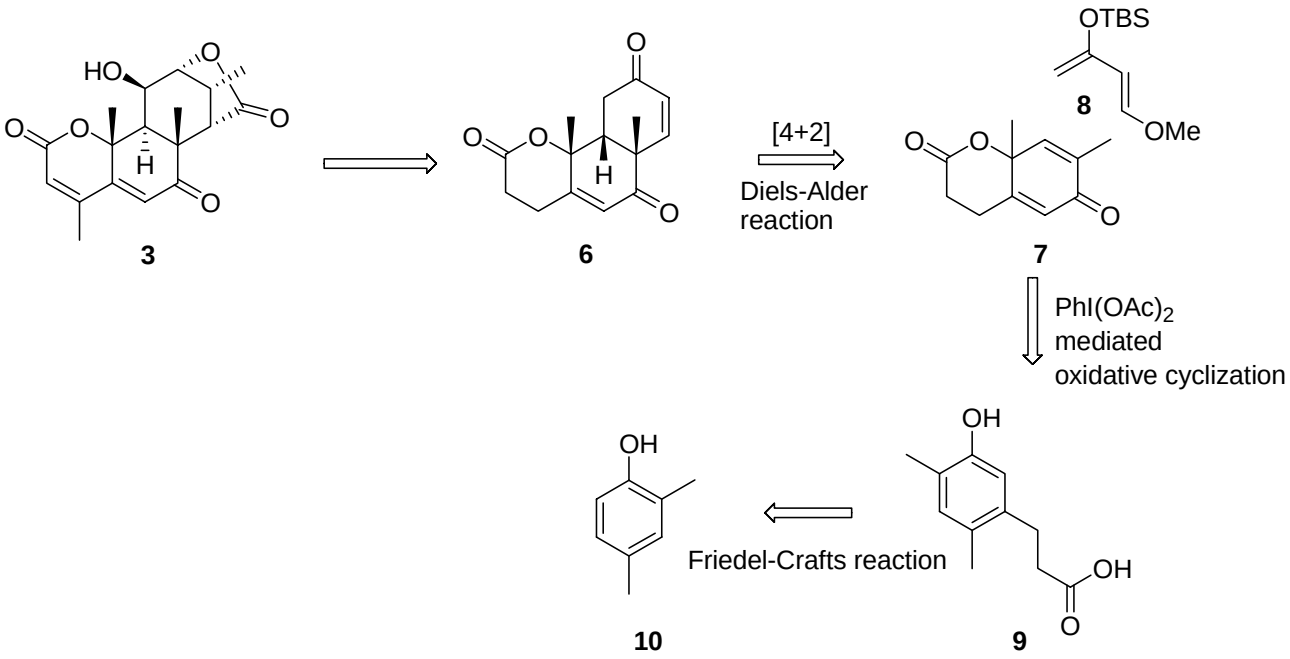
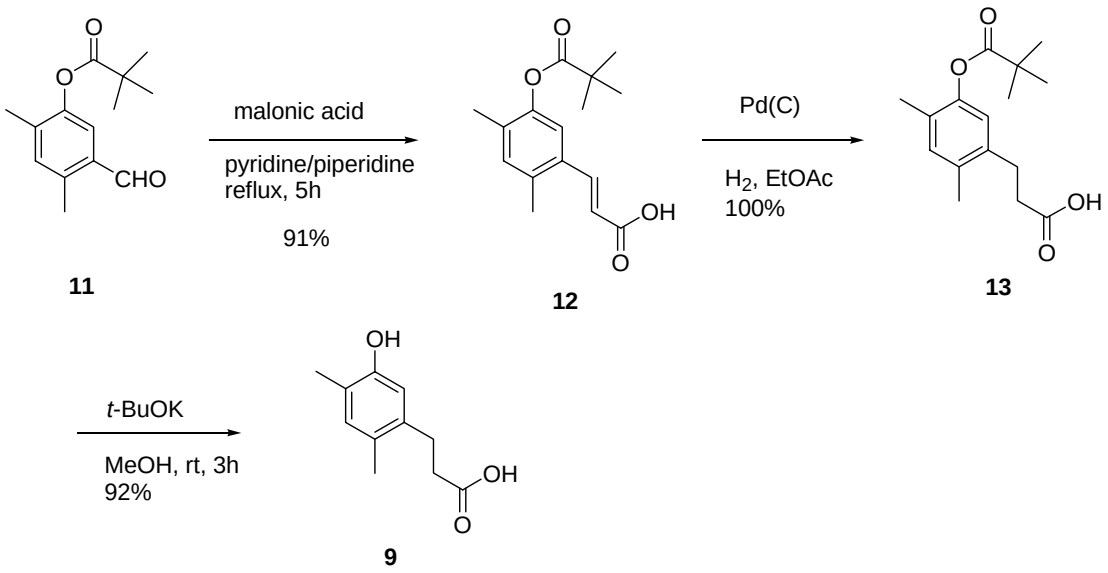


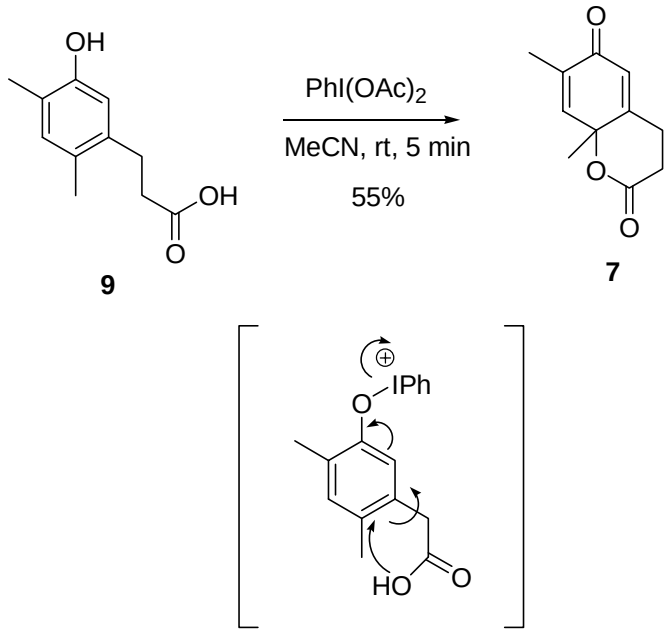
Figure 2

As illustrated in the retrosynthetic analysis (Figure 2), the strategy towards the synthesis of eurycolactone C relied on the Diels-Alder reaction of bicyclic enone **7** and diene **8**. Diels-Alder reaction could produce the tricyclic intermediate **6** with two methyl groups in the axial configuration. Bicyclic compound **7** could be made via iodobenzenediaceatate-mediated intramolecular cyclization reaction from compound **9**.[15] Compound **9** could be generated from commercially available 2,4-dimethylphenol via formylation of 2,4-dimethyl phenyl pivalate,[16] Knoevenagel condensation and reduction of the olefin.



Scheme 1

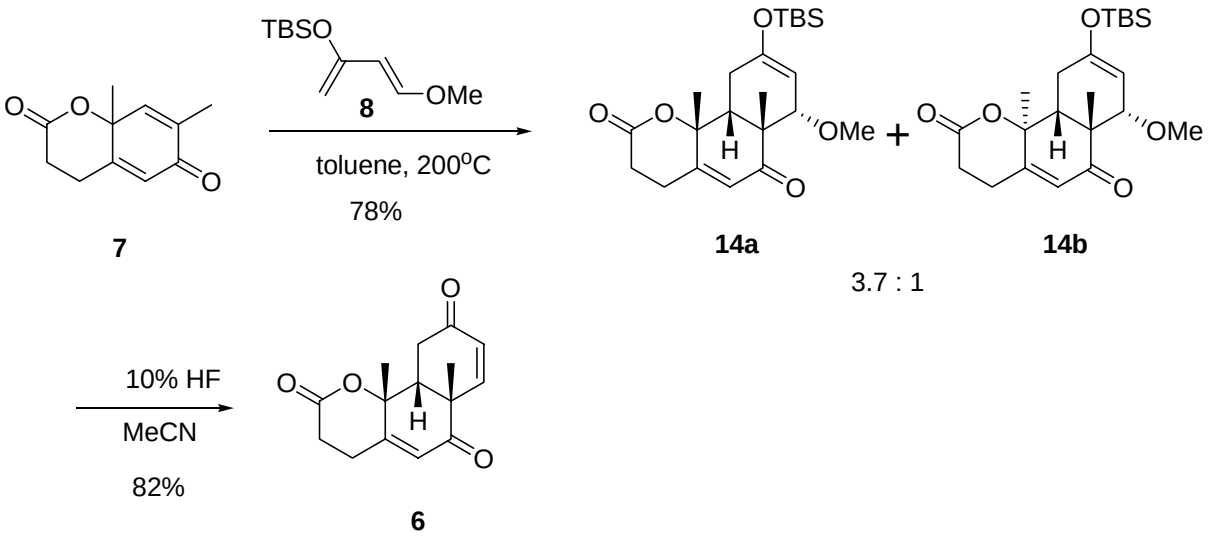
Compound **12** was generated from Compound **11**[16] via a Knoevenagel condensation[17] catalyzed by piperidine. The condensation reaction generated a single *trans*-olefin isomer exclusively. Since the *trans*-isomer **12** could not cyclize via iodobenzenediacetate-mediated intramolecular reaction, the double bond was reduced by Pd(C)-catalyzed hydrogenation to afford compound **13** in quantitative yield. The pivaloyl protecting group of compound **13** was cleaved with *tert*-BuOK in methanol to be ready for the key oxidative intramolecular cyclization.



Scheme 2

With compound **9** in hand, the optimal conditions were examined with changes of solvents, temperature and reaction time. After extensive experimentation, we found that the success of the reaction depended on the proper choice of the solvent. Bicyclic compound **7** was best achieved in acetonitrile.[18]

Various Lewis acids were tested as catalysts in the Diels-Alder reaction of compound **7** with diene **8**. Disappointingly, none of Lewis acids ($BF_3{\cdot}Et_2O$, $ZnCl_2$, $ZnBr_2$, $TiCl_4$ and $AlCl_3$) were successful in generating a Diels-Alder product. Diene **8** could not tolerate the Lewis acidic conditions and decomposed to an enone.



Scheme 3

With the failure with Lewis acid, we investigated thermal conditions for the Diels-Alder reaction. It was found that Diels-Alder reaction of dienophile **7** with diene **8** could occur at 200 ^{o}C for 2 days in a sealed tube to give a tricyclic compounds **14a** and its isomer **14b** in the ratio of 3.7:1. After a flash column purification of the major isomer, enol silyl ether **14a** was converted to enone **6** with 10 % aqueous HF in acetonitrile.

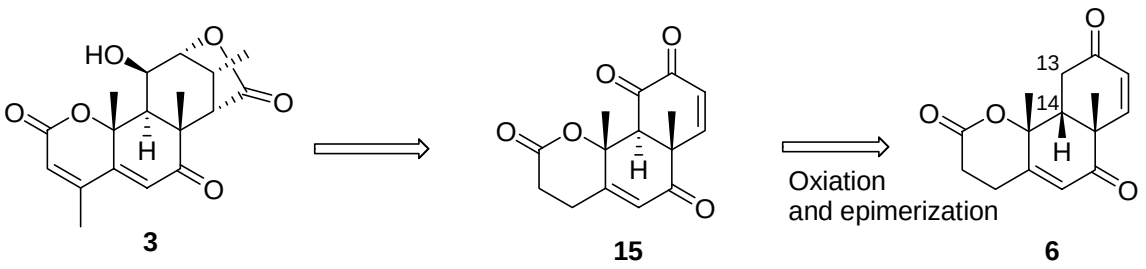
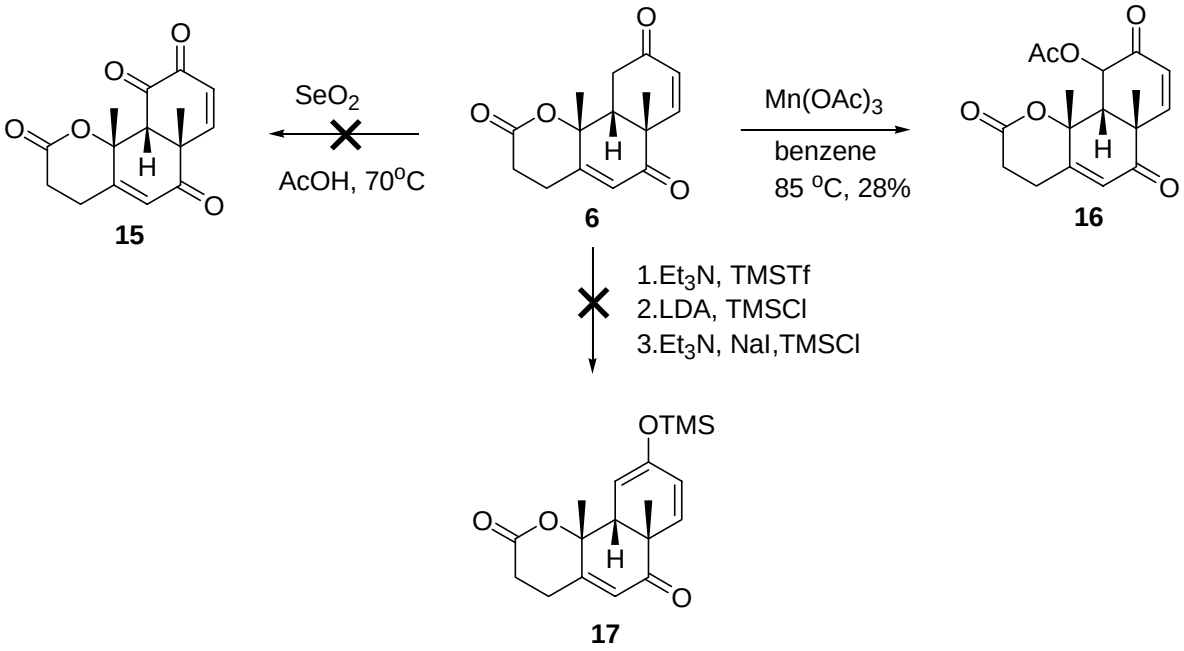


Figure 3

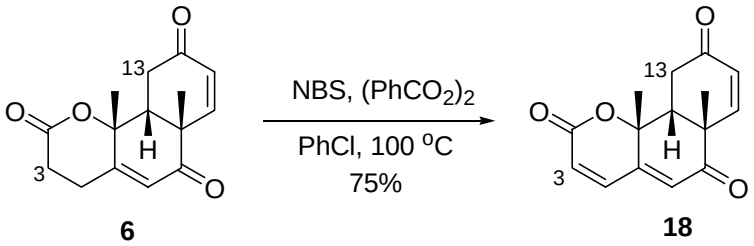
The Diels-Alder reaction successfully generated an advanced intermediate **6** having a tricyclic skeleton with two axial methyl groups. The hydrogen at C-14 needed to be

epimerize. In order to install the desired stereochemistry, we decided to generate diketone **15** (Figure 3).



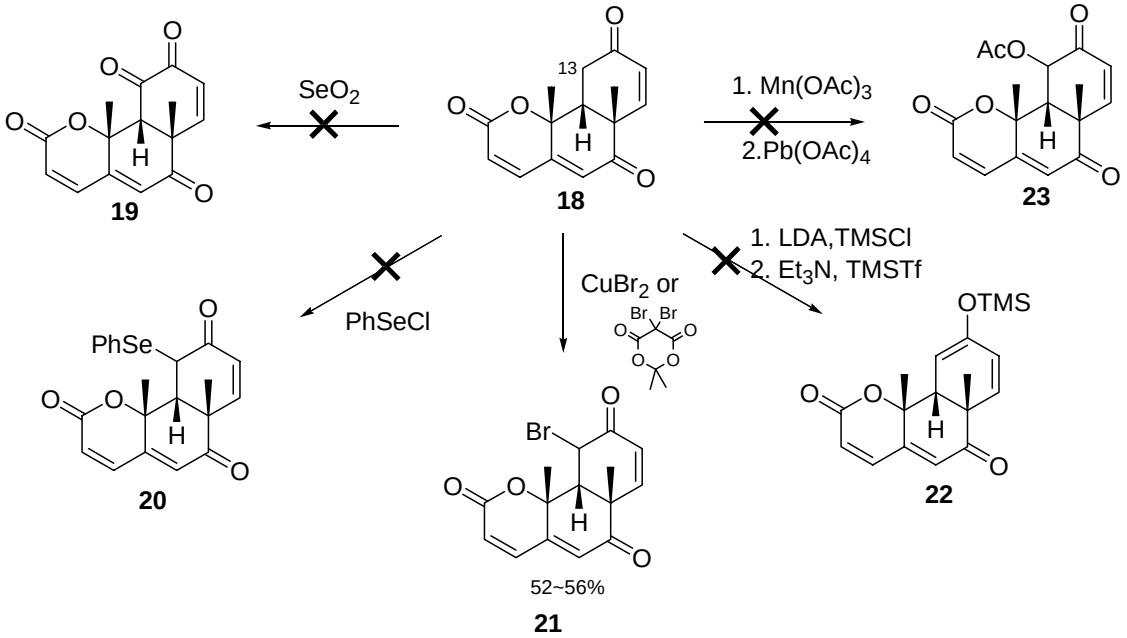
Scheme 4

Direct oxidation of compound **6** with selenium dioxide[19] afforded a complex mixture. Therefore, a stepwise oxidation via the enol silyl ether was examined. Surprisingly, none of silylation reactions produced compound **17**. We found that α-acetoxylation with manganese acetate[20] could generate ketone **16** in 28% yield. However, we could not produce ketone **16** in more than 28% yield, so we decided to search for other routes.



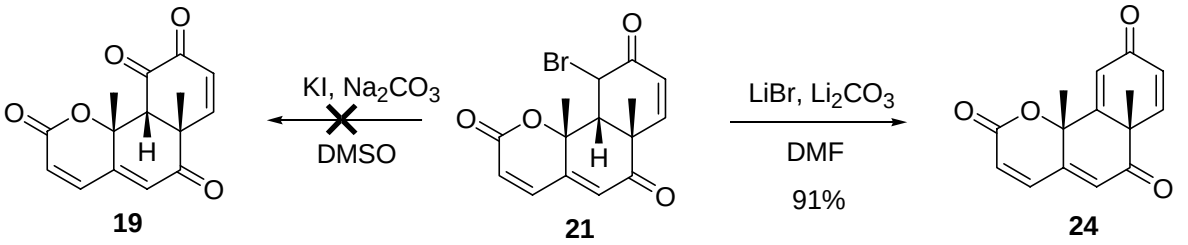
Scheme 5

Tricyclic compound **6** has two different acidic hydrogens at C-3 and C-13. The existence of two different set of acidic hydrogens on compound **6** might cause complex reactions, so we decided to oxidize compound **6** into compound **18** via allylic bromination and elimination. The reaction with *N*-bromosuccinimide and benzoyl peroxide in chlorobenzene gave the desired product **18** in 75% yield. With compound **18** in hand, we tried various reactions to functionalize C-13 (Scheme 6).



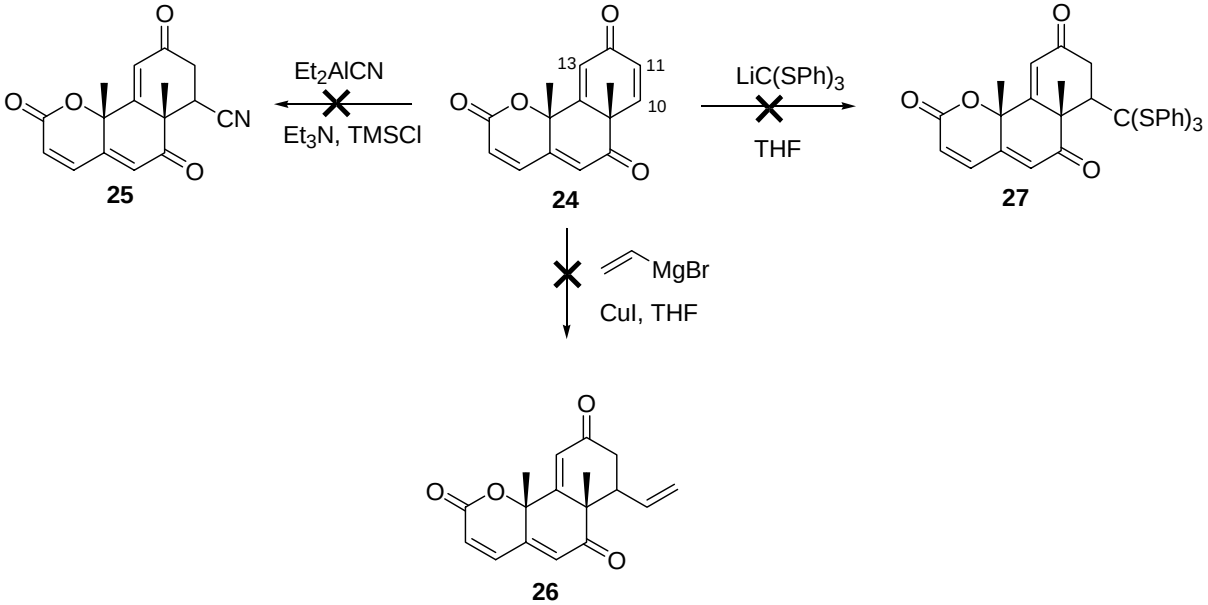
Scheme 6

Among various attempts (SeO_2, PhSeCl, $Mn(OAc)_3$, $Pb(OAc)_4$, LDA / TMSCl and Et_3N/TMSTf) to functionalize C-13, only bromination with $CuBr_2$ or 5,5-dibromoMeldrum's Acid[21] could afford bromide **21** in 56% yield.



Scheme 7

With bromide **21** in hand, we carried out the oxidation of bromoketone **21** to diketone **24** with KI, Na_2CO_3 and DMSO.[22] Unfortunately, we could not isolate diketone **19**. Therefore, we decided to make compound **24**. Treating bromide **21** with LiBr and Li_2CO_3 in DMF provided compound **24** in 91% yield.



Scheme 8

With compound **24** in hand, we envisioned that addition at C-10 could be regioselective due to less steric hinderance for the axial addition. Therefore, we directed our efforts to effect conjugate addition. Unfortunately, none of the attempts (diethylaluminum cyanide, vinyl magnesium bromide and tris(phenylthio)methyl lithium) were successful.

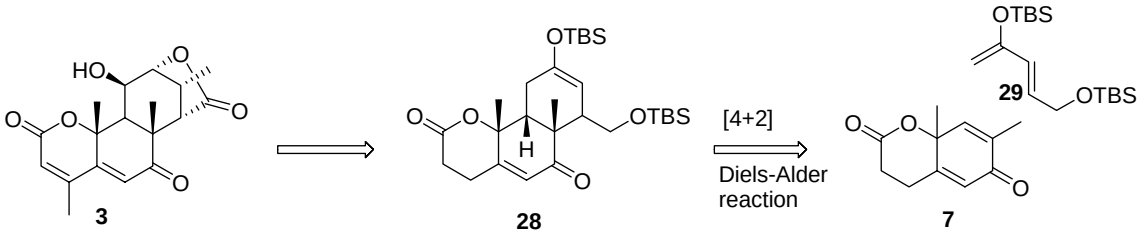
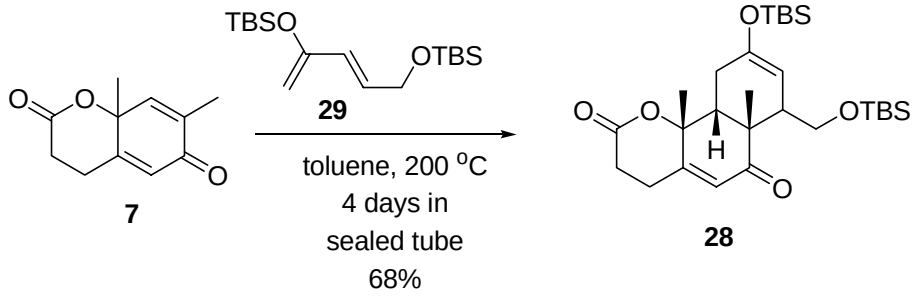


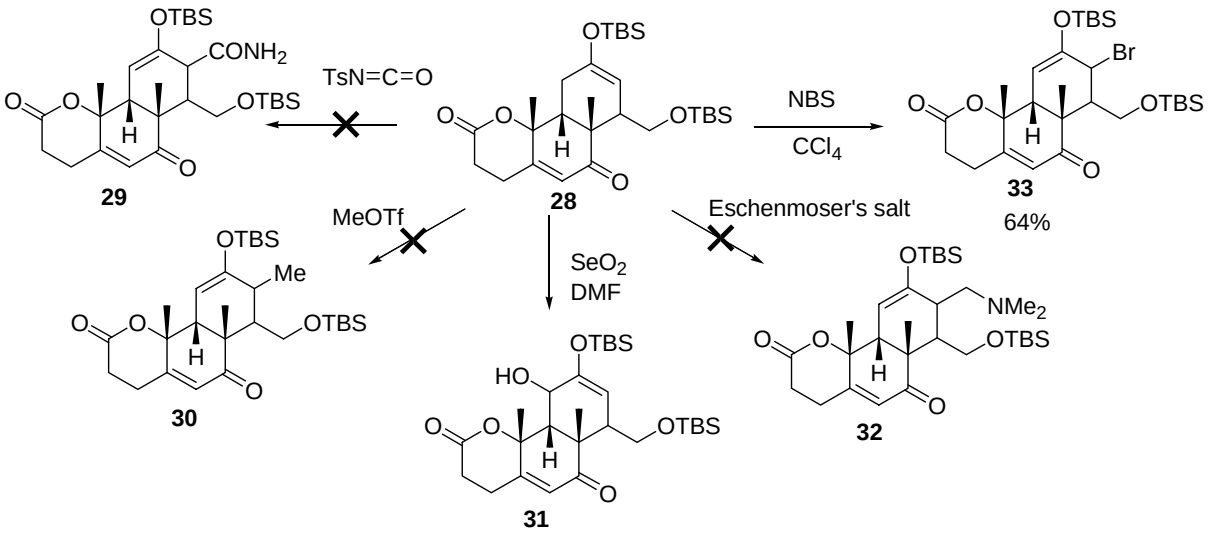
Figure 4

Since we found that the addition to C-10 of compound **24** was not successful, we decided to introduce the group during the Diels-Alder reaction. Therefore, we planned to use diene **29**[23] (Figure 4).



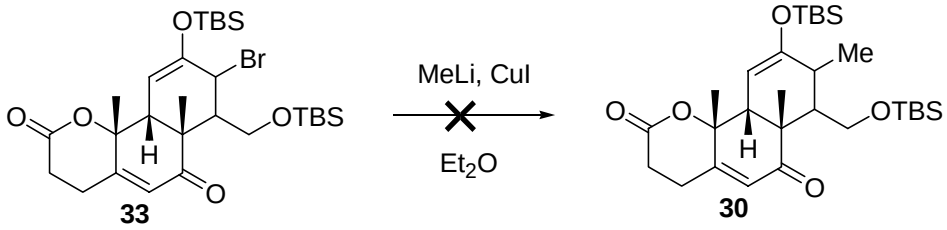
Scheme 9

We carried out the Diels-Alder reaction with new diene **29** to afford product **28** in 68% yield after 4 days at 200°C (Scheme 9).



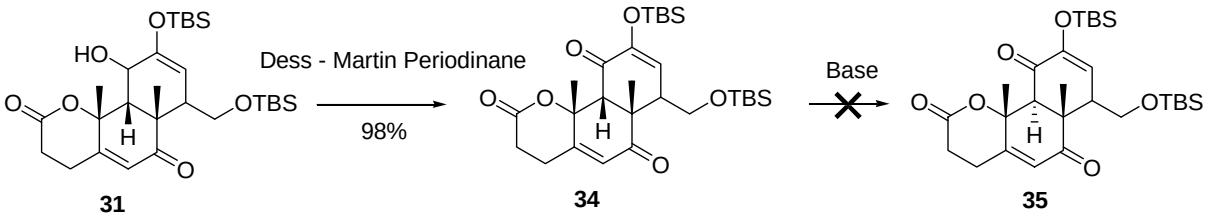
Scheme 10

Magnus[24] reported that enol silyl ethers reacted with electrophiles to provide regioselective and stereoselective products. Therefore, we decided to apply that chemistry to enol silyl ether **28**. Various electrophiles were tested with compound **28** (Scheme 10). Among those electrophilic additions, bromination with NBS and hydroxylation with SeO_2 were successful to provide bromide **33** and alcohol **31**, respectively.



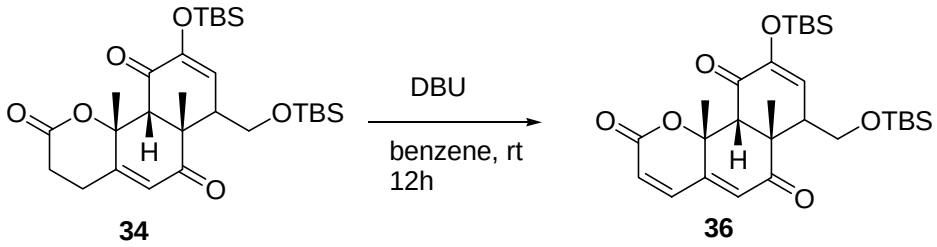
Scheme 11

With bromide **33** in hand, we tried a displacement reaction to generate compound **30**. However, the displacement of bromine with lithium dimethyl cuprate did not provide compound **30**.



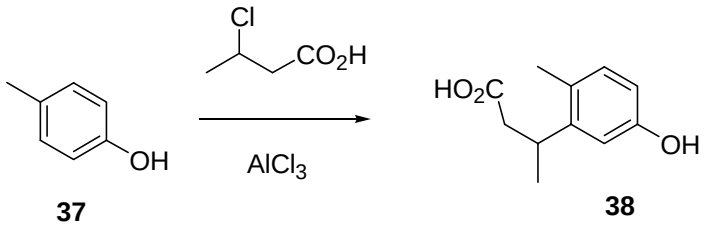
Scheme 12

With compound **31** in hand, we tried to oxidize compound **31** to ketone **34** with Dess-Martin periodinane. To our delight, the oxidation of compound **31** with Dess-Martin periodinane provided ketone **34** in 98% yield. With compound **34**, we attempted epimerization reactions with various bases such as K_2CO_3, *tert*-BuONa, Et_3N and DBU. Unfortunately, the epimerization reactions were not successful. However, the reaction with DBU surprisingly provided an the oxidized compound **36**.



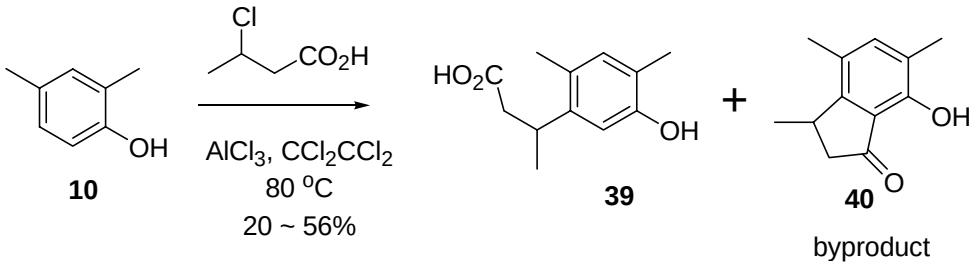
Scheme 13

We found a literature report that a Friedel-Crafts reaction of *p*-cresol and 3-chlorobutyric acid unexpectedly gave the *meta*-alkylated adduct **38** (Scheme 14).[25]



Scheme 14

It was claimed that aluminum chloride reacts with *p*-cresol to generate a bulky aluminum alkoxide to block the *ortho* position of *p*-cresol to allow *meta*-alkylation.



Scheme 15

The Friedel-Crafts reaction of 2,4-dimethylphenol (**10**) with 3-chlorobutyric acid gave compound **39** in 56% yield. We were pleased to find the reaction because compound **39** provided a concise route and a more advanced dienophile **42**. However, we observed that the reaction often gave a poor yield of compound **39**. In order to achieve a reproducible yield, the reaction time and temperature must be controlled with care.

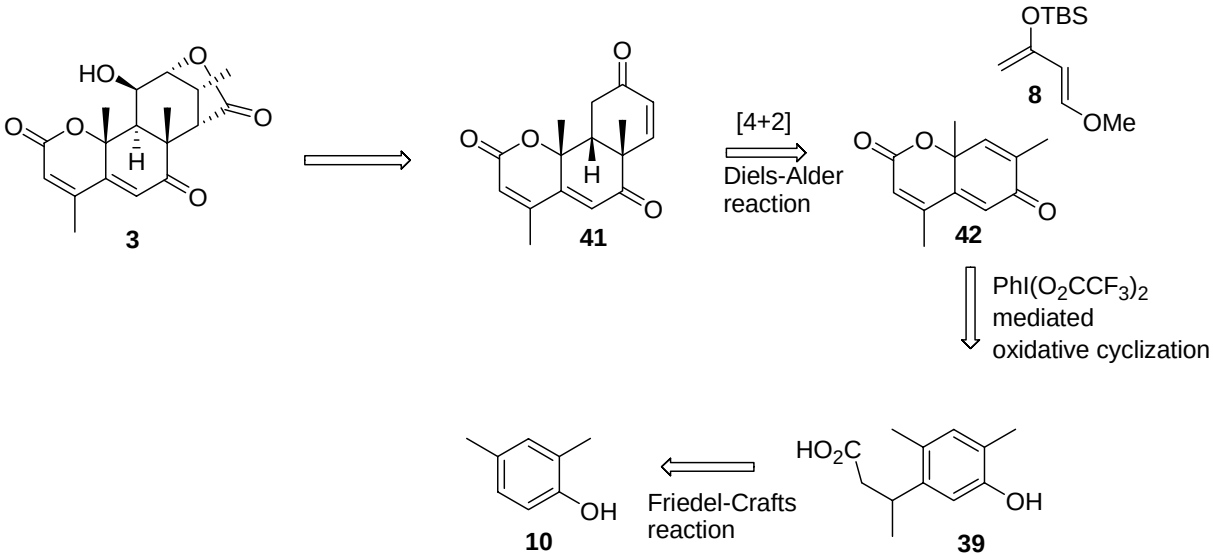
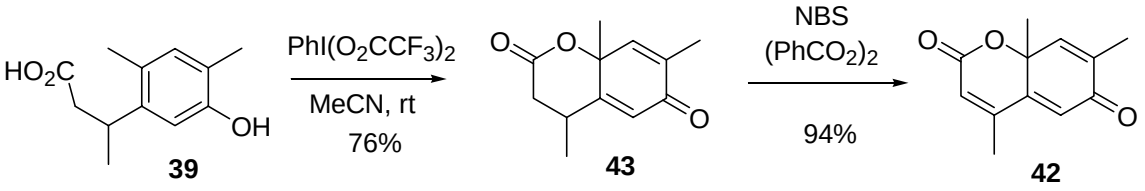


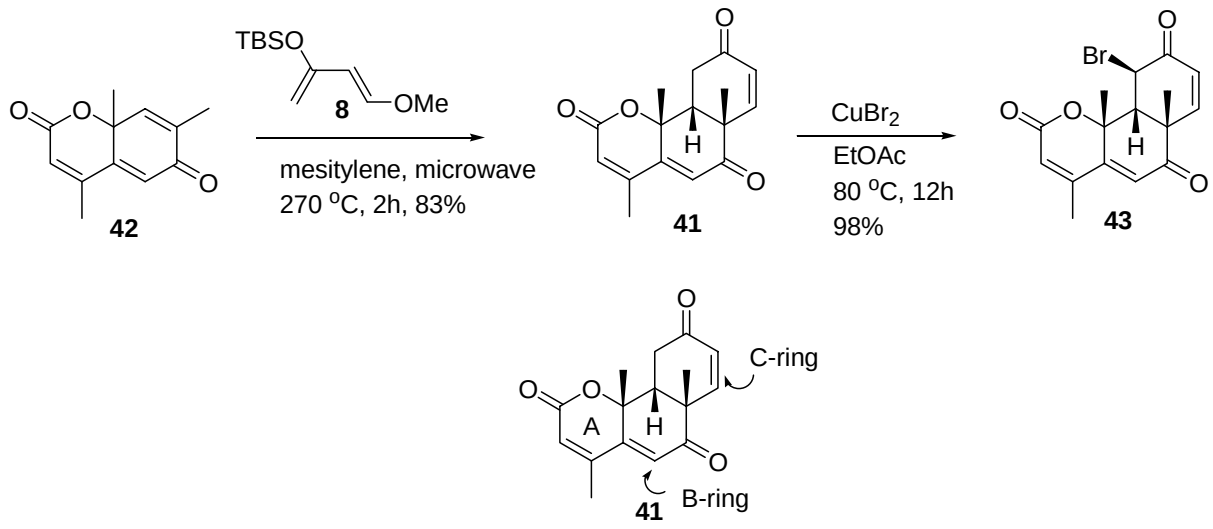
Figure 5

With the successful generation of compound **39**, we could plan a new route toward eurycolactone C (Figure 5).



Scheme 16

With compound **39** in hand, we tried the oxidative cyclization reaction with iodobenzenediacetate. Unfortunately, the reaction only gave a trace amount of product **43**. We observed that changing to iodobenzenebis(trifluoroacetate) formed ketone **43** in 76% yield. The treatment of compound **43** with *N*-bromosuccinimide produced compound **42** by a sequence of bromination and elimination.



Scheme 17

With compound **42** in hand, Diels-Alder reaction was examined. Unfortunately, the reaction did not occur up to 220 °C in a sealed tube. To overcome the failure, the Diels-Alder reaction was carried out in a microwave reactor[26] which is known to give a better result in many cases of thermal Diels-Alder reactions.[27] Several solvents (*N*,*N*-dimethylformamide, benzene, toluene, xylene, 1,2-dichlorobenzene, nitrobenzene and mesitylene) were screened. Mesitylene was found to be the best solvent. The reaction could be achieved at 270 °C in the microwave reactor to give compound **41** in 83 % yield.

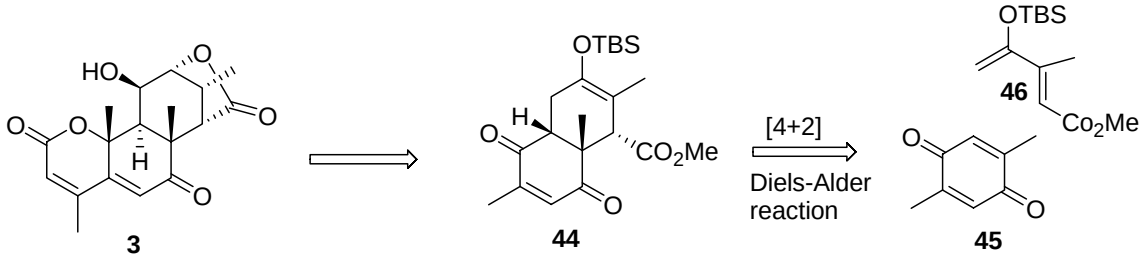
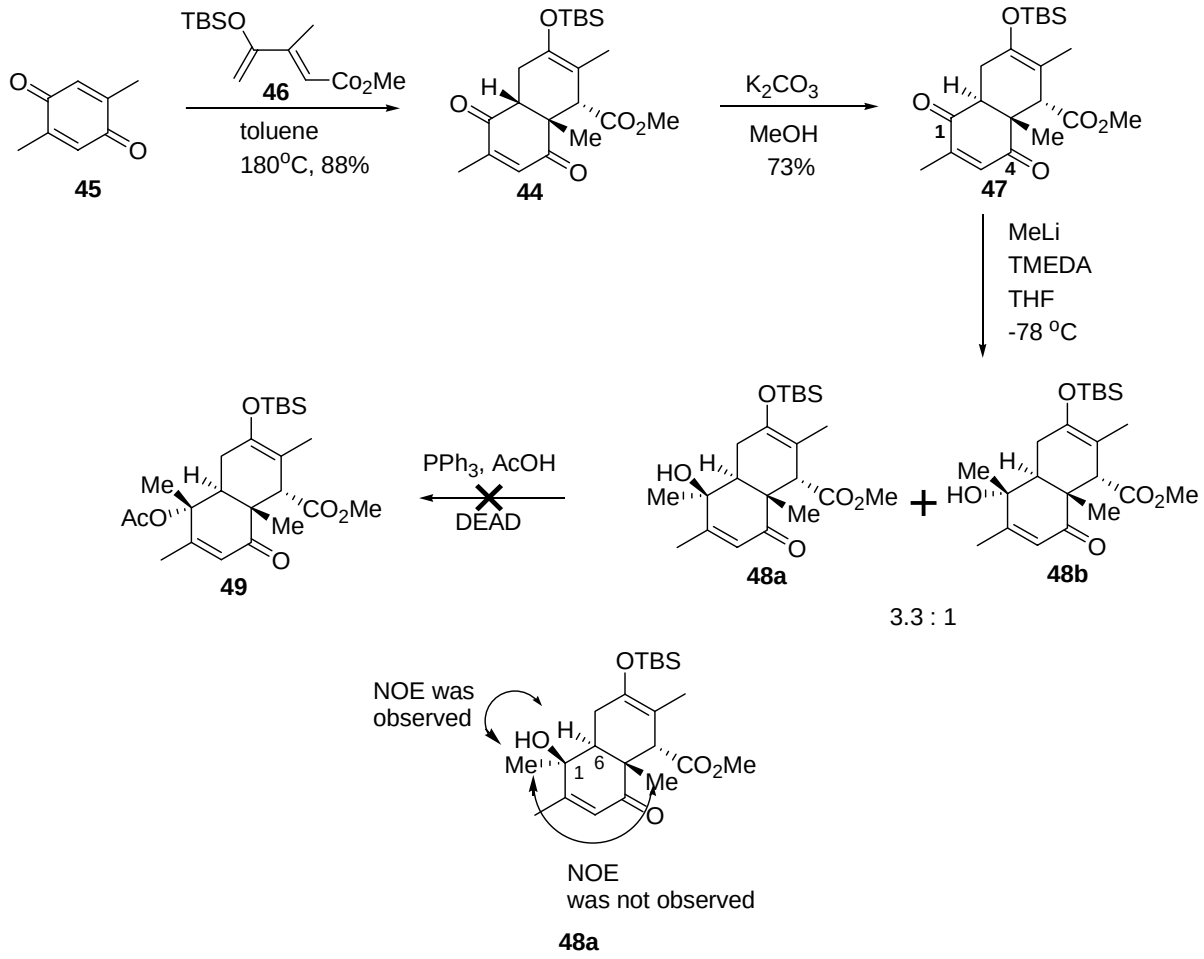


Figure 6

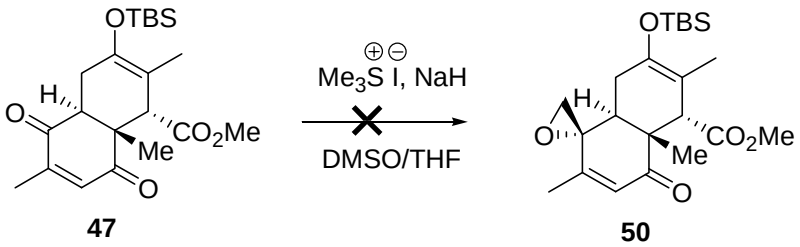
During our efforts to construct the C ring with a correct stereochemistry, we had an alternative plan to complete the synthesis. As shown in Figure 6, a simpler but more reactive dienophile **45** could allow us to use the more advanced diene **46**[28].



Scheme 18

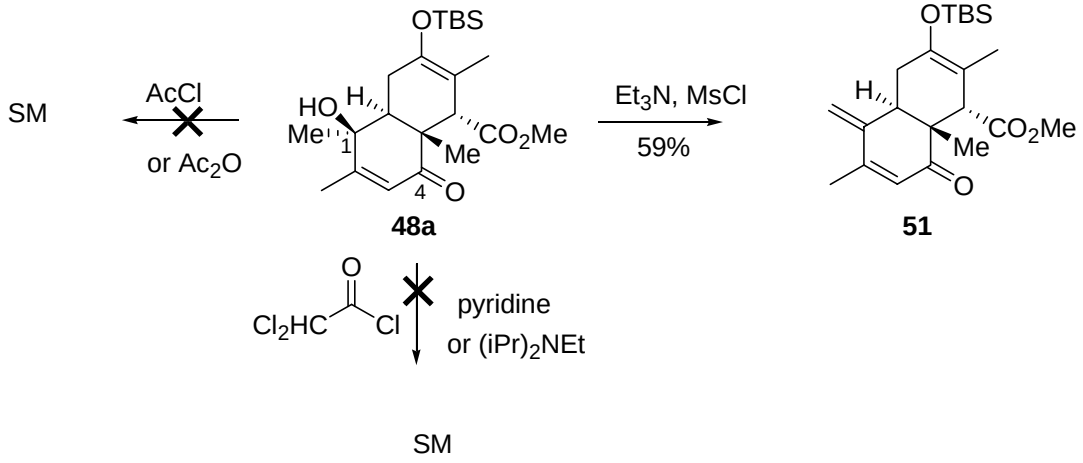
The Diels-Alder reaction of quinone **45** with diene **46** was examined in toluene. Fortunately, the reaction provided bicyclic compound **44** in 88% yield (Scheme 18). Compound **44** was treated with potassium carbonate in methanol to give *trans*-fused compound **47**. With compound **44** in hand, the selective addition of methyl lithium was

investigated. Fortunately, the reaction with methyl lithium in the presence of tetramethylethylenediamine in THF provided compounds **48a** and **48b** in 83% yield. However, the major isomer **48a** has an incorrect stereochemistry due to the equatorial addition of methyl lithium. The stereochemistry of compound **48a** was confirmed by 2D NOESY NMR. The NOESY experiment showed no NOE interaction between two methyl groups but showed an NOE interaction between the methyl group at C-1 and the hydrogen at C-6 (Scheme 18). In order to correct the stereochemistry, we tried a Mitsunobu reaction[29] with acetic acid. However, we could not invert the tertiary alcohol.



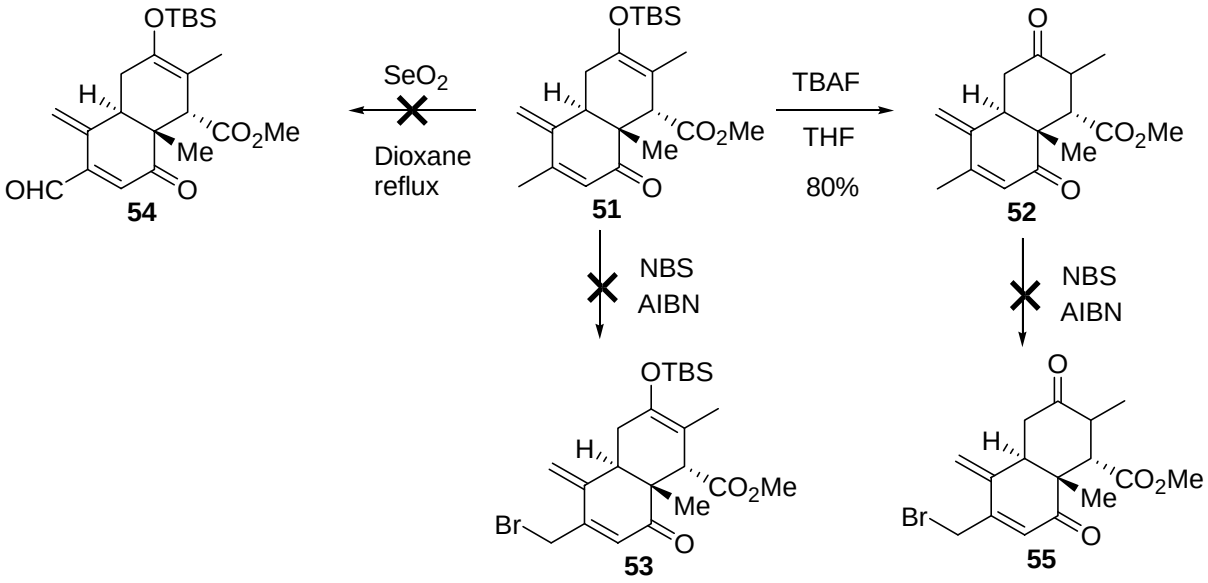
Scheme 19

In order to form the correct stereochemistry, the addition of a neucleophile to ketone **47** should be axial. Corey reported that the reaction of ketones with dimethylsulfonium methylide furnished oxiranes by an axial addition.[30] Therefore, we tried the reaction with ketone **47**. Unfortunately, the reaction did not provide oxirane **50**.



Scheme 20

With the failure to generate oxirane **50**, we planned to convert the alcohol to the acetate. Surprisingly, the acylation of alcohol **48a** with acetyl chloride or acetic anhydride did not occur. Interestingly, the reaction of **48a** with methanesulfonyl chloride formed **51** in 59 % yield.



Scheme 21

With compound **51** in hand, we tried the bromination of compound **51** with *N*-

bromosuccinimide. However, the reaction did not provide bromide **53**. An attempt to oxidize compound **51** to aldehyde **54** was not fruitful, either. We reasoned that the presence of the enol silyl ether group might cause complex reactions. Hence, we decided to cleave the TBS protecting group to generate ketone **52**. Treating compound **51** with tetra-*n*-butylammonium fluoride (TBAF) successfully provided ketone **52** in 80% yield. With compound **52** in hand, we tried the bromination of compound **52**. However, the reaction did not furnish bromide **55**.

In conclusion, our Diels-Alder strategy provided an efficient way to construct the tricyclic skeleton of eurycolactone C. Currently we are investigating the total synthesis of eurycolactone C.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane and benzene were distilled over calcium hydride. All experiments were performed under argon atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.27 ppm for ^1H and 77.23 ppm for ^{13}C), unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were

recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 A, 32-63 μm) was used for a flash column chromatography.

3-[5-(2,2-Dimthylpropionyloxy)-2,4-dimethylphenyl]acrylic acid (12)

To a mixture of compound **11** (1.4 g, 6.0 mmol) and malonic acid (1.2 g, 11 mmol) in pyridine (50 mL) was added piperidine (1 mL) at rt. The reaction mixture was heated to reflux for 5 h. The mixture was poured into ice water (100 mL) containing 1N HCl (20 mL). The resulting precipitate was filtered and washed with water. The precipitate was collected and recrystallized from MeOH/water to afford compound **12** (1.5 g, 5.5 mmol) in 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* =16 Hz, 1H), 7.19 (s, 1H), 7.08 (s, 1H), 6.33 (d, *J* =16 Hz, 1H), 2.41 (s, 3H), 2.15 (s, 3H), 1.40 (s, 9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 171.8, 148.1, 143.6, 135.6, 133.7, 133.0, 131.9, 119.4, 118.4, 114.8, 39.4, 27.4, 19.2, 16.3.

2,2-Dimethylpropionic acid 5-(2-carboxyethyl)-2,4-dimethylphenyl (13)

To a solution of compound **12** (24.9 g, 90.2 mmol) in EtOAc (150 mL) was added Pd(C) (10 g) at rt. The reaction mixture was stirred under H_2 at rt. After being stirred for 1 day, the reaction mixture was filtered through a Celite pad and the organic filtrate was concentrated in vacuo to afford compound **13** (25.1 g, 90.2 mmol) in 100 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.76 (s, 1H), 2.90 (t, *J* = 7.6 Hz, 2H), 2.63 (t, *J* = 7.6 Hz,

2H), 2.27 (s, 3H), 2.10 (s, 3H), 1.38 (s, 9H).

3-(5-Hydroxy-2,4-dimethylphenyl)propionic acid (9)

To a solution of compound **13** (8.23 g, 30.2 mmol) in MeOH (70 mL) and H_2O (70 mL) was added K_2CO_3 (10.42 g, 75.4 mmol) at rt. The reaction was heated to reflux. After being stirred for 12 h, the reaction mixture was neutralized with 1N HCl , extracted with EtOAc, dried over $MgSO_4$, concentrated in v vacuo and purified by flash column chromatography to afford compound **9** (5.73 g, 29.6 mmol) in 98 % yield. ^{1}H NMR (300 MHz, CD_3OD) δ 6.79 (s, 1H), 6.54 (s, 1H), 2.81 (t, *J* = 8.0 Hz, 2H), 2.51 (t, *J* = 8.0 Hz, 2H), 2.16 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 177.1, 154.5, 138.3, 133.7, 127.5, 123.3, 116.0, 35.8, 29.3, 18.4, 15.8.

7,8a-Dimethyl-3,4-dihydro-8a*H*-chromene-2,6-dione (7)

To a solution of compound **9** (4.83 g, 24.9 mmol) in MeCN (100 mL) was added $PhI(OAc)_2$ (8.02 g, 24.9 mmol) at rt under argon. After being stirred for 30 min., the reaction mixture was diluted with Et_2O, washed with sat. $NaHCO_3$, dried over $MgSO_4$, concentrated in vacuo and purified by flash column chromatography to afford compound **7** (2.63 g, 13.7 mmol) in 55 % yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (d, *J* = 1.2 Hz, 1H), 6.17 (d, *J* = 1.8 Hz, 1H), 3.07-2.92 (m, 2H), 2.75-2.61 (m, 2H), 1.92 (d, *J* = 1.5 Hz, 3H), 1.70 (s, 3H).

Compound 14a and 14b

To a solution of dienophile **7** (1.07 g, 5.58 mmol) in toluene (5 mL) was added diene **8** (2.39 g, 11.16 mmol) at rt under argon. The reaction was stirred at 200 ^{o}C in a sealed tube for 24 h. The reaction mixture was cooled to 25 ^{o}C, concentrated in vacuo and purified by flash column chromatography to afford compound **14a** and its isomer **14b** in 78 % yield in the ratio of 3.7:1. **14a** ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (s, 1H), 5.06 (d, *J* = 5.6 Hz, 1H), 3.59 (d, *J* = 5.6 Hz, 1H), 3.05 (s, 3H), 2.95-2.82 (m, 2H), 2.49-2.62 (m, 2H), 2.45-2.38 (m, 1H), 2.26-2.34 (m, 1H), 2.20 (dd, *J* = 7.2 Hz, *J* = 2.4 Hz, 1H), 1.62 (s, 3H), 1.26 (s, 3H), 0.95 (s, 9H), 0.24 (s, 3H), 0.21 (s, 3H). **14b** ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (d, *J* = 1.2 Hz, 1H), 5.16 (d, *J* = 5.2 Hz, 1H), 3.99 (d, *J* = 5.6 Hz, 1H), 3.34 (s, 3H), 2.20-2.98 (m, 7H), 1.86 (s, 3H), 1.36 (s, 3H), 0.88 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H).

Compound 6

To a solution of compound **14a** (2.23 g, 5.49 mmol) in MeCN (100 mL) was added 10% aqueous HF (50 mL) at rt. After being stirred for 3 h, the reaction mixture was diluted with Et_2O, washed with sat. $NaHCO_3$, dried over $MgSO_4$, concentrated in vacuo and purified by flash column chromatography to afford compound **6** (1.17g, 4.50 mmol) in 82 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, *J* = 10 Hz, 1H), 6.89-6.05 (m, 2H), 2.94-2.58 (m, 5H), 2.28 (dd, *J* = 8.4 Hz, *J* = 8.0 Hz, 2H), 1.90 (s, 3H), 1.60 (s, 3H).

Compound 16

To a mixture of compound **6** (0.12 g, 0.45 mmol) and $Mn(OAc)_3$ (1.20 g, 4.55 mmol) was added benzene (8 mL) at rt under argon. The reaction mixture was boiled using a Dean-Stark apparatus. After being stirred for 24 h, the mixture was filtered through a Celite pad, concentrated in vacuo and purified by flash column chromatography to afford compound **16** (40mg, 0.13 mmol) in 28% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, *J* = 10 Hz, 1H), 6.08 (d, *J* = 10 Hz, 1H), 6.03 (d, *J* = 1.2 Hz, 1H), 5.84 (d, *J* = 2.8 Hz, 1H), 3.07-2.90 (m, 2H), 2.82 (d, *J* = 2.8 Hz, 1H), 2.64-2.52 (m, 2H), 2.05 (s, 3H), 1.98 (s, 3H), 1.62 (s, 3H).

Compound 18

To a solution of compound **6** (0.14 g, 0.51 mmol) in chlorobenzene (5 mL) was added NBS (0.11 g, 0.62 mmol) followed by benzoyl peroxide (0.012 g, 0.051 mmol) at rt. The reaction mixture was heated into 100 ^{o}C under argon. After being stirred for 1 h, the mixture was diluted with Et_2O, washed with sat. $NaHCO_3$, dried over $MgSO_4$, concentrated in vacuo and purified by flash column chromatography to afford compound **18** (0.10 g, 0.38 mmol) in 75% yields. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 10 Hz, 1H), 6.83 (d, *J* = 10 Hz, 1H), 6.32 (d, *J* = 10 Hz, 1H), 6.18 (s, 1H), 6.08 (d, *J* = 10 Hz, 1H), 2.96-2.83 (m, 2H), 2.24 (dd, *J* = 13.2 Hz, *J* = 2.8 Hz, 1H), 1.94 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 196.4, 160.7, 154.1, 149.1, 140.1, 128.1, 127.8, 125.4, 81.6, 50.0, 47.4, 37.3, 32.0, 28.5; HRMS *m/e* (EI) for $C_{15}H_{14}O_4$ $(M)^+$ calcd 258.0892, measured 258.0900.

Compound 21

Method A : To a solution of compound **18** (17 mg, 65 μmol) in EtOAc (1 mL) and $CHCl_3$ (1 mL) was added $CuBr_2$ (16 mg, 71 μmol) at rt. The reaction mixture was heated into 85 ^oC to reflux under argon. After being stirred for 24 h, the reaction was filtered, was concentrated in vacuo and purified by flash column chromatography to afford compound **20** (12 mg, 36 μmol) in 56 % yield.

Method B: To a solution of compound **18** (47 mg, 181 μmol) in CCl_4 (2 mL) was added dibromoMeldrum's Acid (55 mg, 181 μmol) at rt. The reaction mixture was heated to reflux under argon. After being stirred for 12 h, the reaction was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$, dried over $MgSO_4$, concentrated in vacuo and purified by flash column chromatography to afford compound **21** (32 mg, 96 μmol) in 53 % yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, J = 9.6 Hz, 1H), 7.05 (d, J = 10.4 Hz, 1H), 6.31 (d, J = 9.6 Hz, 1H), 6.13 (s, 1H), 6.11 (d, J = 10.4 Hz, 1H), 4.85 (d, J = 3.2 Hz, 1H), 3.14 (d, J = 3.2 Hz, 1H), 1.98 (s, 3H), 1.63 (s, 3H).

Compound 24

To a solution of bromide **21** (34 mg, 0.101 mmol) in DMF (6 mL) was added LiBr (18 mg, 0.20 mmol) followed by Li_2CO_3 (22 mg, 0.303 mmol) at rt under argon. The reaction mixture was heated to reflux. After being stirred for 3 h, the solution was diluted with Et_2O,

washed with water, dried over $MgSO_4$, concentrated in vacuo and purified by flash column chromatography to afford compound **24** (23 mg, 0.091 mmol) in 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 10 Hz, 1H), 7.19 (d, *J* = 10 Hz, *J* = 0.8 Hz, 1H), 6.90 (d, *J* = 2.0 Hz, 1H), 6.39-6.36 (m, 2H), 6.19 (s, 1H), 2.05 (s, 3H), 1.69 (s, 3H)

Compound 28

To a solution of dienophile **7** (0.19 g, 0.99 mmol) in toluene (5 mL) was added diene **29** (0.65 g, 1.99 mmol) at rt under argon. The reaction was stirred at 200 ^{o}C in a sealed tube for 4 days. The reaction mixture was cooled to 25 ^{o}C, concentrated in vacuo and purified by flash column chromatography to afford compound **28** (0.35g, 0.673 mmol) in 68 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (d, *J* = 1.2 Hz, 1H), 4.89 (t, *J* = 1.2 Hz, 1H), 3.85 (dd, *J* = 10 Hz, *J* = 4.8 Hz, 1H), 3.78 (dd, *J* = 10 Hz, *J* = 8 Hz, 1H), 2.98-2.18 (m, 8H), 1.83 (s, 3H), 1.39 (s, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.13 (s, 3H), 0.12(s, 3H), 0.06 (s, 3H), 0.04 (s, 3H).

Compound 31

To a solution of compound **26** (12 mg, 24 μmol) in DMF (2 mL) was added SeO_2 (3 mg, 29 μmol) at rt under argon. After being stirred at rt for 1day, the mixture was filtered, diluted with Et_2O, washed with water several times, dried over $MgSO_4$, concentrated in vacuo and purified by flash column chromatography to afford compound **29** (5 mg, 10 μL) in 42% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (s, 1H), 5.00 (d, *J* = 4.4 Hz, 1H), 4.29 (s, 1H), 3.51-3.42

(m, 2H), 3.08-2.96 (m, 2H), 2.76-2.53 (m, 2H), 2.44-2.39 (m, 2H), 1.82 (s, 3H), 1.45 (s, 3H), 0.96 (s, 9H), 0.86 (s, 9H), 0.22 (s, 3H), 0.21(s, 3H), -0.01 (s, 3H), -0.03 (s, 3H).

Compound 33

To a solution of compound **28** (14 mg, 27 μmol) in CCl_4 (3 mL) was added NBS (5 mg, 27 μmol) at rt under argon. After being stirred at rt for 12 h., the mixture was filtered, concentrated in vacuo and purified by flash column chromatography to afford compound **31** (10 mg, 17 μL) in 64% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (s, 1H), 5.08 (d, *J* = 1.8 Hz, 1H), 4.40 (dd, *J* = 11.1 Hz, *J* = 7.2 Hz, 1H), 3.32 (dd, *J* = 10.2 Hz, *J* = 2.4 Hz, 1H), 4.02 (dd, *J* = 11.1 Hz, *J* = 1.2 Hz, 1H), 2.98-2.80 (m, 4H), 2.61-2.46 (m, 2H), 1.92 (s, 3H), 1.49(s, 3H), 0.90 (s, 18H), 0.11 (s, 3H), 0.11(s, 3H), 0.08 (s, 3H), 0.03 (s, 3H).

Compound 34

To a solution of compound **31** (2.7 mg, 5.0 μmol) in $CHCl_2$ (1 mL) was added Dess-Martin periodinane (7.2 mg, 16.5 μmol) at 0 ^{o}C. After being stirred for 16 h at rt, the reaction mixture was concentrated in vacuo and purified by flash column chromatography to afford compound **34** (2.6 mg, 4.9 μmol) in 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (d, *J* = 1.6 Hz, 1H), 6.07 (d, *J* = 5.6 Hz, 1H), 3.53 (d, *J* = 7.2 Hz, 2H), 3.12-2.96 (m, 2H), 2.80-2.51 (m, 4H), 1.87 (s, 3H), 1.41 (s, 3H), 0.97 (s, 9H), 0.86 (s, 9H), 0.22 (s, 3H), 0.19(s, 3H), -0.01 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 190.7, 167.8, 150.7, 147.7,

127.6, 125.7, 64.2, 59.0, 48.3, 45.2, 30.8, 29.9, 28.2, 26.4, 26.0, 25.9, 25.7, 18.6, 18.3, -4.3, -4.5, -5.3, -5.3; HRMS *m/e* (EI) for $C_{28}H_{46}O_6Si_2$ $(M)^+$ calcd 534.2833, measured 534.2844.

Compound 36

To a solution of compound **34** (7 mg, 13 μmol) in benzene (4 mL) was added DBU (4 mg, 26 μmol) at rt. After being stirred for 12 h, the reaction mixture was concentrated in vacuo and purified by flash column chromatography to afford compound **36** (5 mg, 9.1 μmol) in 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 10 Hz, *J* = 0.8 Hz, 1H), 6.23 (s, 1H), 6.20 (dd, *J* = 10 Hz, *J* = 0.8 Hz, 1H), 5.98 (d, *J* = 6 Hz, 1H), 3.50-3.37 (m, 2H), 2.87 (s, 1H), 2.62-2.58 (m, 1H), 1.89 (s, 3H), 1.42 (s, 3H), 0.97 (s, 9H), 0.84 (s, 9H), 0.24 (s, 3H), 0.22 (s, 3H), -0.03 (s, 3H), -0.07 (s, 3H).

2-(5-Hydroxy-2,4-dimethylphenyl)propionic acid (39) and 7-Hydroxy-3,4-trimethylindan-1-one (40)

To a suspension of $AlCl_3$ (26.8 g, 201 mmol) in CCl_2CCl_2 (150 mL) was added 2,4-dimethyl phenol (8.2 g, 67 mmol) dropwise followed by 3-chlorobutyric acid (8.17 g, 67 mmol) at rt under argon. The solution was heated to 85 ^{o}C. After being stirred for 3 h at 85 ^{o}C, the mixture was poured into ice water. The mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, concentrated in vacuo and purified by flash column chromatography to afford compound **39** in 56% yield and byproduct **40**. **Compound 39:** ^{1}H

NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.62 (s, 1H), 3.49-3.41 (m, 1H), 2.64 (dd, *J* = 2.4 Hz, *J* = 15.6 Hz, 1H), 2.52 (dd, *J* = 4.8 Hz, *J* = 15.6 Hz, 1H), 2.26 (s, 3H), 2.19 (s, 3H), 1.24 (d, *J* = 6.8 Hz, 3H). **Indanone 40:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.15 (s, 1H), 3.48-3.39 (m, 1H), 2.98 (dd, *J* = 19.2 Hz, *J* = 7.2 Hz, 1H), 2.32 (dd, *J* = 19.2 Hz, *J* = 2.0 Hz, 1H), 2.28 (s, 3H), 2.22 (s, 3H), 1.33 (d, *J* = 6.8 Hz, 3H).

4,7,8a-Trimethyl-3,4-dihydro-8a*H*-chromene-2,6-dione (43)

To a solution of compound **39** (86 mg, 0.41 mmol) in MeCN (5 mL) was added $PhI(O_2CCF_3)_2$ (178 mg, 0.41 mmol) at rt. After being stirred for 15 min, the solution was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$, concentrated in vacuum and purified by flash column chromatography to afford compound **43** in 76 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ6.74 (s, 1H), 6.15 (s, 1H), 3.15-3.03 (m, 1H), 2.97 (dd, *J* = 6 Hz, 17.6 Hz, 1H), 2.24 (dd, *J* = 12.8 Hz, 17.6 Hz, 1H), 1.91 (s, 3H), 1.68 (s, 3H), 1.26 (d, *J* = 6 Hz, 3H).

4,7,8a-Trimethyl-8a*H*-chromene-2,6-dione (42)

To a solution of compound **43** (43 mg, 0.21 mmol) in chlorobenzene (5 mL) was added NBS (41 mg, 0.23 mmol) followed by benzoyl peroxide (15 mg, 0.063 mmol) at rt. The reaction mixture was heated to 100 ^{o}C and stirred for 20 min. The mixture was diluted with ethyl ether and wash with saturated $NaHCO_3$. The organic layer was concentrated in vacuo

and purified by flash column chromatography to afford compound **42** in 94 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (q, *J* = 1.2 Hz, 1H), 6.37 (s, 1H), 6.08 (q, *J* = 1.2 Hz, 1H), 2.18 (d, *J* = 1.2 Hz, 3H), 1.93 (d, *J* = 1.2 Hz, 3H), 1.69 (s, 3H).

Compound 41

To a solution of compound **42** in mesitylene (1 mL) was added diene (30 μL) at rt in sealed tube. The solution was heated to 270 ^{o}C for 2 h under 20~60 *psi* pressure in a microwave reactor. After 2 hours the solution was concentrated in vacuo and purified by flash column chromatography to afford compound **41** in 83 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, *J* = 10 Hz, 1H), 6.28 (s, 1H), 6.18 (s, 1H), 6.08 (d, *J* = 10 Hz, 1H), 2.89 (m, 2H), 2.26-2.18 (m, 4H), 1.90 (s, 3H), 1.64 (s, 3H)

Compound 43

To a solution of compound **41** (57 mg, 0.21 mmol) in ethyl acetate (5 mL) was added $CuBr_2$ (140 mg, 0.63 mmol) at rt. The solution was heated to reflux for 24 h under argon. After being cooled to rt, the solution was filtered, concentrated in vacuo and purified by flash column chromatography to afford compound **43** in 98 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.05 (d, *J* = 10.4 Hz, 1H), 6.23 (s, 1H), 6.18 (s, 1H), 6.07 (d, *J* = 10.4 Hz, 1H), 4.89 (d, *J* = 3.2 Hz, 1H), 3.13 (d, *J* = 3.2 Hz, 1H), 2.20 (d, *J* = 1.2 Hz, 3H), 1.95 (s, 3H), 1.63 (s,

3H).

Compound 44

To a solution of 2,5-dimethylbenzoquinone **45** (24 mg, 0.179 mmol) in toluene (5 mL) was added diene **46** (68 mg, 0.266 mmol) at rt under argon. The reaction mixture was heated in a sealed tube at 180 ^{o}C. After being stirred for 12 h at 180 ^{o}C, the reaction mixture was concentrated in vacuo and purified by flash column chromatography to afford compound **44** (62 mg, 0.158 mmol) in 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (d, *J* =1.6 Hz, 1H), 3.48 (s, 3H), 3.15 (dd, *J* = 17.6 Hz, *J* = 1.6 Hz, 1H), 2.97 (s, 3H), 2.81 (dd, *J* = 8.0 Hz, *J* = 1.6 Hz, 1H), 2.25-2.17 (m, 1H), 2.00 (d, *J* =1.6 Hz, 3H), 1.56 (t, J = 1.6, 3H), 1.44 (s, 3H), 0.99 (s, 9H), 0.24 (s, 3H), 0.20 (s, 3H).

Compound 47

To a solution of compound **44** (0.88 g, 2.23 mmol) in MeOH (100 mL) was added K_2CO_3 (0.31 g, 2.23 mmol) at rt. After being stirred for 1 h at rt, the reaction mixture was diluted with Et_2O, neutralized with 1N HCl, washed with brine, dried over $MgSO_4$, concentrated in vacuo and purified by flash column chromatography to afford compound **47** (0.64g, 1.63 mmol) in 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (q, *J* =1.6 Hz, 1H), 4.23 (dd, *J* = 10.4 Hz, *J* = 2.4 Hz, 1H), 3.70 (s, 3H), 3.17 (S, 1H), 2.46-2.35 (m, 2H), 2.03 (d, *J* = 1.6 Hz, 3H), 1.74(t, *J* = 1.6Hz, 3H), 1.11 (s, 3H), 0.98 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H).

Compound 48a and 48b

To a solution of compound **47** (0.15 g, 0.38 mmol) in THF (20 mL) at -78 ^{o}C under argon was added TMEDA (0.32 g, 2.73 mmol) followed by MeLi (0.33 mL, 0.46 mmol, 1.4 M in Et_2O). After being stirred for 30 min at -78 ^{o}C, the reaction mixture was quenched with water, diluted with Et_2O, washed with brine, dried over $MgSO_4$, concentrated in vacuo and purified by flash column chromatography to afford compound **48a** and its isomer **48b** in 83% yield in the ratio of 3.3:1. **48a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (d, *J* =1.6 Hz, 1H), 3.63 (s, 3H), 3.21 (dd, *J* = 11.6 Hz, *J* = 5.6 Hz, 1H), 3.11 (s, 1H), 2.52-2.41 (m, 1H), 2.23 (dd, *J* =4.8 Hz, *J* = 16.8 Hz, 1H), 2.04 (d, *J* = 1.6, 3H), 1.72 (s, 3H), 1.42 (s, 3H), 1.17 (s, 3H), 0.97 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H). **48b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (d, *J* =1.6 Hz, 1H), 3.64 (s, 3H), 3.33 (dd, *J* = 12.0 Hz, *J* = 5.2 Hz, 1H), 3.14 (s, 1H), 2.42-2.33 (m, 1H), 2.31-2.20 (m, 1H), 2.07 (d, *J* = 1.2, 3H), 1.72 (s, 3H), 1.38 (s, 3H), 1.09 (s, 3H), 0.97 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H).

Compound 51

To a solution of compound **48a** (18 mg, 46 μmol) in CH_2Cl_2 (5 mL) was added Et_3N (19 mg, 184 μmol) followed by MsCl (11 mg, 92 μmol) at 0 ^{o}C. After being stirred for 1 h at rt, the reaction mixture was poured into sat. $NaHCO_3$, diluted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, concentrated in vacuo and purified by flash column chromatography to afford compound **51** (10 mg, 27 μmol) in 59% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5, 85

(s, 1H), 5.54 (d, *J* =2.0 Hz, 1H), 5.24 (s, 1H), 4.00-3.91 (m, 1H), 3.66 (s, 3H), 3.21 (s, 1H), 2.32-2.26 (m, 2H) , 2.10 (d, *J* = 0.8 Hz, 3H), 1.72 (s, 3H), 0.98 (s, 9H), 0.78 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 174.8, 154.2, 145.1, 144.5, 126.0, 115.4, 107.4, 52.7, 51.8, 47.5, 39.1, 30.7, 26.1, 20.6, 18.5, 18.2, 15.7, -3.2, -3.6.

Compound 52

To a solution of compound **51** (54 mg, 143 μmol) in THF (2 mL) was added TBAF (0.157 mL, 157 μmol, 1M solution in THF) at 0 ^{o}C. After being stirred for 10 min, the reaction mixture was diluted with Et_2O, washed with brine, dried over $MgSO_4$, concentrated in vacuo and purified by flash column chromatography to afford compound **47** (32 mg, 114 μmol) in 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5, 82 (s, 1H), 6.56 (d, *J* =1.6 Hz, 1H), 5.20 (d, *J* = 1.2 Hz, 1H), 4.13-4.05 (m, 1H), 3.64 (s, 3H), 3.34 (d, J = 6.4 Hz, 1H), 2.83-2.74 (m, 1H), 2.70-2.53 (m, 2H), 2.09 (d, *J* = 1.2 Hz, 3H), 1.28 (s, 3H), 1.05 (d, J = 6.8 Hz, 3H).

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GENERAL CONCLUSIONS

In this dissertation, we have investigated direct and concise strategies for biologically important natural products.

Chapter 1 described the regioselectivity of electrophilic aromatic substitutions on pivalates and triflates of multi-substituted phenols. The use of aryl triflates and pivalates to control the regiochemistry of intermolecular acylation, bromination or alkylation should have broad application in organic synthesis.

Chapter 2 described the novel methodology to provide 6- or 8-substituted 1-methoxy-naphthalenes (or α-naphthols).

Chapter 3 described synthetic studies towards eurycolactone C. The core tricyclic skeleton of the natural product was synthesized using the intermolecular Diels-Alder reaction as the key step.

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